Neurobiological correlates of mindfulness-related interventions in healthy persons and patients with acute and remitted depression

Thesis (cumulative thesis)
Presented to the Faculty of Arts and Social Sciences
of the University of Zurich
for the degree of Doctor of Philosophy
by

Sarah Hildegard Karen Opialla
from Kiel, Germany

Accepted in the Fall Semester 2014
on the Recommendation of the Doctoral Committee:
Prof. Dr. rer.nat. Lutz Jäncke (main advisor)
Prof. Dr. rer.nat. Boris Quednow

Zurich, 2014

Acknowledgement

Foremost, I would like to gratefully thank my supervisors Prof. Dr. Lutz Jäncke, Prof. Dr. Boris Quednow and Prof. Dr. Uwe Herwig for giving me the opportunity to undertake this doctoral thesis and for their professional support. A special thank goes to PD Dr. Annette Beatrix Brühl for her mentoring and scientific guidance. Besides my advisors, I would like to thank all my co-workers in the research group "Emotion Regulation" at the Psychiatric University Hospital Zurich, and especially my dear colleague and friend Sigrid Scherpiet. Finally, my thanks go to all subjects who participated in the presented studies.

Original articles included in this doctoral thesis

Study 1: Opialla, S., Herwig, U., Scherpiet, S., Hittmeyer, A., Cattapan, K., Jäncke, L., Brühl, A.B. (2014). Neural correlates of self-reflection and emotion introspection in patients with acute and remitted depression: an intrasubject comparison (submitted to *Psychiatry Research: Neuroimaging*).

Study 2: Opialla, S., Lutz, J., Scherpiet, S., Hittmeyer, A., Jäncke, L., Rufer, M., Grosse Holtfort, M., Herwig, U., Brühl, A.B. (in press). Neural circuits of emotion regulation: A comparison of mindfulness-based and cognitive reappraisal strategies (accepted for publication in *European Archives of Psychiatry and Clinical Neuroscience*).

Table of contents

I. Summary

Mindfulness, the „awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment" (Kabat-Zinn, 2003) is a concept with increasing impact on psychological well-being. Mindfulness has its roots in ancient eastern traditions close to Buddhism, it has been implemented in the treatment of diverse psychiatric and physical disorders and proven its efficacy (Chiesa & Serretti, 2010). Nevertheless, its mode of action remains indistinct, with neuropsychological research pointing to distinct neural activation patterns depending on the investigated sample and the conceptualization of mindfulness. Studies indicate some involvement of lateral prefrontal areas and reduced amygdala activation during mindfulness (Burklund, Creswell, Irwin, & Lieberman, 2014; Herwig, Kaffenberger, Jäncke, & Brühl, 2010; Lieberman et al., 2007) but reveal mixed results for the direction of ventro- and dorsomedial prefrontal activation (Dickenson, Berkman, Arch, & Lieberman, 2013; Farb et al., 2007).

This doctoral thesis further investigates the neural correlates of mindfulness interventions. As part of a large ongoing research project on emotion regulation, the first study build on a previous work of our research group, that investigated neural correlates of self-reflection compared to emotion introspection. We found decreased amygdala activation during the mindfulness-close emotion introspection in healthy subjects, pointing to an ability of untrained subjects to engage in mindfulness (Herwig, Kaffenberger, Jäncke, & Brühl, 2010). The first study used the same paradigm but performed a within-subject comparison of acutely and remitted depressed patients. As a main finding, we revealed that emotion introspection was associated with reduced amygdala and VMPFC activation compared to self-reflection in both states, pointing to the ability of patients in the acutely and remitted depressed state to engage in mindfulness. Furthermore, the remitted state was associated with increased DLPFC activation during self-reflection compared to the acutely depressed state, which was characterized by increased activation of the right amygdala. This could indicate that a

controlled reflection process replaces the automated rumination during self-reflection in the course of remission.

The second study compared mindful and cognitive emotion regulation during the anticipation and perception of emotional stimuli in healthy subjects. Results indicate that both strategies trigger a similar network of activation of the DMPFC, anterior MPFC and the amygdala (compare Buhle et al., 2013; Kalisch, 2009; Burklund et al., 2014). Additionally the anticipation of negative compared to neutral stimuli was associated with stronger activation in ventro- and dorsolateral prefrontal areas, supramarginal gyrus and the left insula in the mindfulness group (compare Herwig et al., 2010; Zhang, et al. 2012; Ochsner & Gross, 2008; Dickenson et al., 2013; Morin & Hamper, 2012). We concluded that the early initiation of mindfulness during the anticipation of emotional stimuli recruits more neural resources, whereas both interventions recruit similar resources during the perception, pointing to a comparable emotion regulating effect.

In summary, the results reported in this doctoral thesis add insight to the relatively young research on neural correlates of mindfulness, pointing to the ability of even untrained healthy people as well as people suffering from major depression to engage in basic mindfulness interventions.

II. Zusammenfassung

Achtsamkeit wird definiert als die „Bewusstheit, die dadurch entsteht, dass die Aufmerksamkeit absichtsvoll, im gegenwärtigen Moment, nicht-wertend auf die sich von Moment zu Moment entfaltende Erfahrung gerichtet wird" (Kabat-Zinn, 2003) und bezeichnet ein Konzept, dass mit psychischem Wohlbefinden in Zusammenhang gebracht wird. Das Konzept der Achtsamkeit hat seine Wurzeln in fernöstlichen Traditionen, welche dem Buddhismus nahe sind und findet auf Grund seiner Wirksamkeit zunehmend Eingang in die Behandlung zahlreicher psychiatrischer und körperlicher Erkrankungen (review: Chiesa & Serretti, 2010). Die genaue Wirkungsweise von Achtsamkeit ist jedoch noch unklar, wobei neuropsychologische Forschungsergebnisse auf spezifische neuronale Aktivierungsmuster in Abhängigkeit von der untersuchten Stichprobe und der Konzeptualisierung des Konstrukts hindeuten. Bisherige Studienergebnisse zeigen während Achtsamkeit übereinstimmend eine Beteiligung lateral präfrontaler Areale sowie eine verminderte Aktivierung der Amygdala (Burklund, Creswell, Irwin, & Lieberman, 2014; Herwig, Kaffenberger, Jäncke, & Brühl, 2010; Lieberman et al., 2007). Widersprüchliche Ergebnisse zeigten sich für die Aktivierung ventro- und dorsomedial präfrontaler Areale (Dickenson, Berkman, Arch, & Lieberman, 2013; Farb et al., 2007).

Die vorliegende Dissertation hatte daher zum Ziel, die neuronalen Korrelate von Achtsamkeitsinterventionen weiter zu untersuchen. Die enthaltenen Studien sind Teil eines umfangreichen, laufenden Forschungsprojekts zur Emotionsregulation. Die erste Studie baut auf eine vorherige Arbeit auf, bei der neuronale Korrelate von Selbstreflexion und Emotionsintrospektion bei gesunden Probanden untersucht wurden. Hier zeigte sich bei der achtsamkeitsnahen Emotionsintrospektion eine verminderte Aktivierung der Amygdala. Dies deutet darauf hin, dass bereits untrainierte Probanden in der Lage sind eine achtsame Haltung einzunehmen (Herwig et al., 2010). Die erste Studie verwendete dasselbe Paradigma und untersuchte eine Gruppe von Patienten im akut depressiven Zustand sowie im remittierten Zustand. Ein

Hauptergebnis war hier, dass die Emotionsintrospektion verglichen mit der Selbstreflexion mit reduzierter Amygdala- und VMPFC-Aktivierung assoziiert ist. Dies deutet darauf hin, dass Patienten in beiden Zuständen, akut depressiv und remittiert, in der Lage sind Achtsamkeit zu praktizieren. Im remittierten Zustand zeigte sich zudem eine stärkere DLPFC-Aktivität bei kognitiver Selbstreflexion verglichen mit dem akut depressiven Zustand, der durch eine erhöhte Aktivierung der rechten Amygdala gekennzeichnet war. Dies könnte darauf hindeuten, dass ein bewusster Reflexionsprozess die automatisierte Rumination während kognitiver Selbstreflexion im Verlauf der Remission ersetzt.

Die zweite Studie verglich achtsame und kognitive Emotionsregulation während der Erwartung und Betrachtung emotionaler Stimuli bei gesunden Probanden. Die Ergebnisse zeigten, dass beide Strategien ein ähnliches neuronales Netzwerk aus DMPFC, anteriorem MPFC und Amygdala aktivierten (vergl. Buhle et al., 2013; Kalisch, 2009; Burklund et al., 2014). Zusätzlich war die Erwartung negativer Stimuli im Vergleich zu neutralen Stimuli bei der Anwendung einer achtsamen Haltung mit erhöhter Aktivierung in ventro- und dorsolateralen präfrontalen Arealen, dem supramarginalen Gyrus und der linken Insula assoziiert (e.g. Herwig et al., 2010; Zhang, et al. 2012; Ochsner & Gross, 2008; Dickenson et al., 2013; Morin & Hamper, 2012). Es wird daher angenommen, dass die frühe Initiierung von Achtsamkeit während der Erwartung emotionaler Stimuli mehr neuronale Ressourcen erfordert, wohingegen beide Interventionen während der Betrachtung ähnliche Areale aktivierten. Dies deutet auf einen vergleichbaren Effekt in Bezug auf die Emotionsregulation hin. Zusammenfassend lässt sich festhalten, dass die im Rahmen dieser Doktorarbeit durchgeführten Studien neue Einblicke in das relativ junge Forschungsfeld der neuronalen Korrelate von Achtsamkeit gibt. Die Ergebnisse zeigen, dass sowohl untrainierte gesunde Probanden als auch Patienten mit einer depressiven Erkrankung einfache Achtsamkeitsinterventionen ausführen können.

1. Introduction

1.1. Emotion regulation

Emotion regulation is central in everyday life, as we are constantly confronted with events or stimuli that evoke emotional reactions. Emotion regulation has been defined as adaptive, if it changes the emotional response in the desired way or when the long-term benefits out weight the costs of short-term changes in emotion (Werner & Gross, 2010, p. 19). According to the well-established process model of emotion regulation, different emotion regulation strategies are used at different time-points in the process of emotion regulation (Gross & Thompson, 2007, p. 10, compare Figure 1).

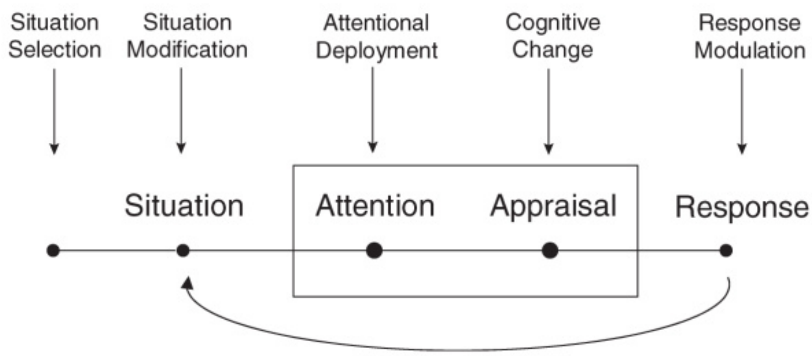

Figure 1 "A process model of emotion regulation that highlights five families of emotion regulation strategies." from "Handbook of emotion regulation", edited by James J. Gross, Copyright 2007. Copyright Guilford Press. Reprinted with permission of The Guilford Press.

On the one hand, there are strategies aiming for changes concerning the situation before the emotional response occurs, defined as antecedent-focused. Specifically, people can influence to which situations they expose themselves. They can try to modify the external situation after it has occurred, they can decide where they set their focus of attention and which meaning they give the situation. On the other hand, response-focused emotion regulation strategies aim for changes of the emotional response after it occurred. Response-focused strategies can influence the emotional experiences, expression or physiological responding, for example by intensifying, diminishing, prolonging or curtailing it (Gross, 1998).

Research on emotion regulation strategies has placed its main emphasis on the investigation of reappraisal as a strategy often taught in psychotherapeutic treatments (review: Aldao, Nolen-Hoeksema, & Schweizer, 2010). Reappraisal is defined as "actively reinterpreting the meaning of an emotionally evocative stimulus in ways that lessen its emotional punch" (Ochsner & Gross, 2007, p. 98). It is frequently opposed to strategies that are mainly regarded as rather maladaptive, particularly suppression (Gross, 1998; Gross & John, 2003; Henry, Rendell, Green, McDonald, & O'Donnell, 2008). On the neurobiological level, successful emotion regulation has been associated with increased activation of lateral and medial prefrontal areas and decreased amygdala responses (Buhle et al., 2013; Diekhof, Geier, Falkai, & Gruber, 2011; Goldin, McRae, Ramel, & Gross, 2008; Herwig et al., 2007; Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; Kohn et al., 2014; Ochsner, Bunge, Gross, & Gabrieli, 2002). Nevertheless, precise networks involved in different emotion regulation strategies, assumed as adaptive, remain indistinct as direct comparisons are still rare (Burklund, Creswell, Irwin, & Lieberman, 2014).

1.2. Disturbed emotion regulation in depressive disorders

Impaired emotion regulation is a core deficit in major depressive disorders, manifested in depressed mood and decreased interest and energy for most of the time for at least two weeks (World Health Organization, 2012). Moreover, depression is characterized by high relapse rates and the risk of chronification (Ramana et al., 1995). According to Beck, major depression is characterized by a negative bias towards the future, the world and the self (Beck, Rush, Shaw, & Emery, 1979, p. 11). Neuropsychological research supports that patients with major depressive disorder have a pessimistic attitude towards events of unknown valence (Herwig et al., 2010). This pessimistic bias has been associated with increased dorsolateral prefrontal (DLPFC) and medial prefrontal (MPFC) activation in comparison to healthy controls. In addition, self-focus in depression has been associated with increased ventral or dorsal prefrontal activation (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012; Northoff, 2007). Furthermore, the ability to down-regulate sad feelings seems to be impaired, reflected by increased activation in right dorsal anterior cingulate (ACC), temporal areas and the right amygdala and insula (Beauregard, Paquette, & Lévesque, 2006). Becks cognitive model of depression was further supported by evidence for the negative cognitive biases on the neurobiological level. Disner and colleagues (Disner, Beevers, Haigh, & Beck, 2011) reviewed studies based on the components of Becks model. They proposed an integrated cognitive neurobiological model of depression, describing an increased influence of subcortical emotion processing regions along with reduced activations in regions associated with cognitive control.

According to Werner and Gross (Werner & Gross, 2010, p. 21) and within the framework of the process model of emotion regulation, individuals with mental disorders such as depression can show dysfunctional behaviours at diverse time-points during the emotion regulation process. For example, the avoidance of challenging situations hinders the person from making new, potentially positive experiences and thus prevents from learning how to handle such situations and how to perceive themselves as efficient.

A theoretical link between Beck's model (1979) and the process model (Gross & Thompson, 2007) can be made using the general emotion model as implemented in dialectical behaviour therapy (Bohus & Wolf-Arehult, 2011, p. 184, compare Figure 2). The model assumes that emotional vulnerability can be regarded as an upstream process to the perception of the emotional situation, influencing one's abilities to deal with the situation. Examples for emotional vulnerabilities in healthy people are lack of sleep, having a cold and other. Therefore, I propose to regard major depression along with the described biases (Beck et al., 1979) as the emotional vulnerability, influencing the ability to regulate a person’s emotions at the distinct time-points according to the process model (Gross & Thompson, 2007).

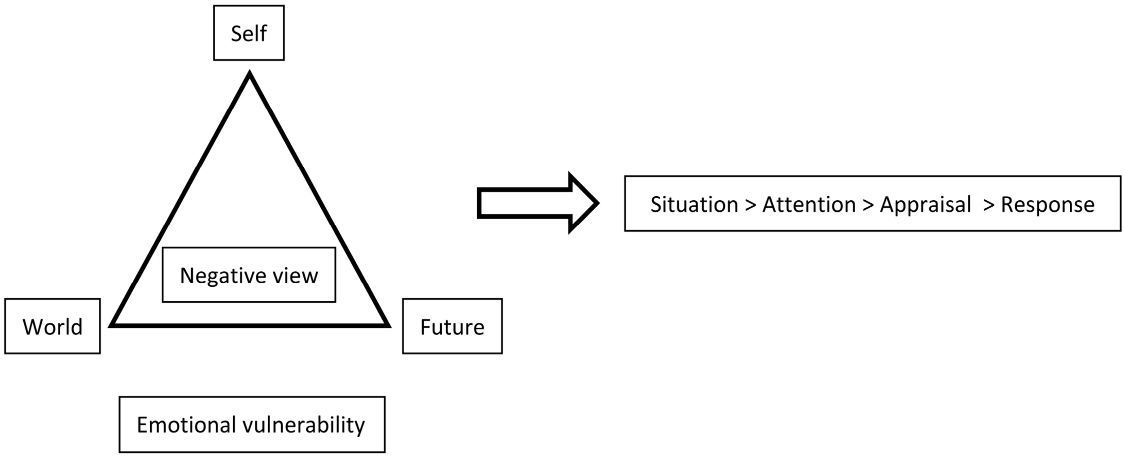

Figure 2 Integration of the cognitive model of depression (Beck et al., 1979), the concept of emotional vulnerability (Bohus and Wolf-Arehult, 2011) and the process model of emotion regulation (Gross & Thompson, 2007).

In the following, two distinct ways of dealing with arising emotions - cognitive emotion regulation and mindfulness - will be discussed specifically with respect to depression and embedded into the context of the treatment of depressive disorders and with special regard to the neurobiological correlates. Additionally, an overview is given over the concept of mindfulness and its application in the psychotherapeutic context.

1.3 Cognitive emotion regulation

Cognitive emotion regulation strategies such as reappraisal, an important element of cognitive and behavioural therapy (Beck et al., 1979; Ellis, 2008), have been in the focus of recent research on emotion regulation. Within the process model of emotion regulation, they can be labelled as antecedent-focused emotion regulation strategies (Gross & Thompson, 2007). Empirical support for the effectiveness of cognitive emotion regulation strategies are derived from several reviews and meta-analysis

(Chambless & Ollendick, 2001; Webb, Miles, & Sheeran, 2012). Cognitive therapy has been successful in the treatment of acute depression as well as in relapse prevention (Beck & Dozois, 2011; van Aalderen et al., 2012) Additionally, it has been successfully implemented in the treatment of bipolar disorder, specific phobias, social phobia and panic disorder (Beck & Dozois, 2011; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012).

On the neurobiological level, studies point to a regulation of subcortical areas such as the amygdala, by prefrontal cortical regions, especially dorsolateral (DLPFC), ventrolateral (VLPFC) and dorsomedial (DMPFC) areas extending into the pre-supplemental motor area (preSMA) when cognitive emotion regulation is performed (Buhle et al., 2013; Kalisch, 2009; Ochsner & Gross, 2008). Contrary, a positive association between ventromedial prefrontal and amygdala activation was found in depressive patients (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007).

1.4. Mindfulness

The concept of mindfulness has its roots in ancient eastern traditions close to Buddhism. Mindfulness can be described as “the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment” (Kabat-Zinn, 2003). Most techniques taught in psychotherapy directly address emotion regulation and thus have a determined goal, for example the use of a skills box for stress reduction in borderline disorder (Linehan, 1993). In contrast to these techniques, mindfulness is regarded as “a way of being that takes ongoing effort to develop and refine it” (Kabat-Zinn, 2003). In practice, it is highly challenging because one needs to let go of its personal anticipations, goals and aspirations (Kabat-Zinn, 2003).

Furthermore and contrary to cognitive emotion regulation strategies that attempt to modify affective experiences, mindfulness attempts to modify ones relationship to the personal experience (Chambers et al., 2014; Chambers, Lo, & Allen, 2008). This is opposed to an intuitive understanding of emotion regulation, as the evolutionary imprinting insists on fight, flight or freeze when confronted by emotional stimuli. Borkovec names it “a paradoxical and strange way to live” that one has to let go of the desired outcomes to finally get them (Borkovec, 2002). Thus, it becomes obvious why mindfulness has to be developed over time, and why regular practice on a daily basis is essential (Kabat-Zinn, 2003).

The described aspects make it difficult to define mindfulness as an emotion regulation strategy or to classify it as antecedent-focused or response-focused and integrate it into the process-model proposed by Gross and Thompson (2007). Brühl (2012) calls mindfulness a strategy that influences the development of an emotion during the whole process of an emotional reaction. It shapes all aspects from the perception to the initial evaluation to the reaction (Brühl, 2012; Chambers et al., 2008). This description fits very well with the conceptualization of mindfulness as a general attitude that influences not only certain aspects of one’s daily life, but our whole being.

Several researchers have tried to enhance insight into the concept of mindfulness by proposing theoretical models. Thus, Bishop and colleagues (2004) propose a two-component model of mindfulness with the components self-regulation of attention and orientation towards experience. From their point of view, mindfulness does not intend to create a particular state or to regulate ones emotions, but to regulate ones attention (Bishop et al., 2004). Shapiro and colleagues (2006) propose three axioms, namely intention, attention and attitude based on the definition of mindfulness by Kabat-Zinn (2003). Compared to Bishop and colleagues (2004), their model adds the component of intention, meaning the cause why someone engages in mindfulness practice (Shapiro et al., 2006). They reason, that this component is crucial for the understanding of the process of mindfulness and for the development of increased dispositional mindfulness. Nevertheless, Shapiro and colleagues (2006) clearly emphasize that their model is “a” model and that a lot of research is required to clarify the nature of mindfulness and its mode of action.

It has to be carefully taken into account that – contrary to the field of emotion regulation where the process model (Gross & Thompson, 2007; Hamilton, 1960) is well established - there is no clear consensus regarding the conceptualization of mindfulness yet. Studies differ strongly in the theoretical background they build upon and in their conceptualization of mindfulness. Some studies investigate mindfulness as a trait and others as a state concept (Creswell, Way, Eisenberger, & Lieberman, 2007; Herwig et al., 2010; Lutz et al., 2014; Shapiro, Brown, Thoresen, & Plante, 2011). However, it is important to note that these two do not mutually exclude each other, but influence one another (Chiesa, 2013).

A growing body of literature has investigated the beneficial effects of mindfulness on psychological well-being (Brown & Ryan, 2003; Chiesa & Serretti, 2010). It has been associated e.g. with increased immune functioning, reduced distress, enhanced self-insight, interpersonal benefits such as increases relationship satisfaction and improved emotion regulation (Davis & Hayes, 2011). Within the context of psychiatric treatments, mindfulness techniques are increasingly implemented in programs focusing on the improvement of emotion regulation capabilities, as taught in dialectical behaviour therapy of borderline personality disorder (Linehan, 1993) or in the treatment of acute and remitted depression (Segal, Williams, & Teasdale, 2013).

MBCT as well as mindfulness based stress reduction (MBSR) are usually taught in an eight-week group therapy. It includes the training of mindful body perception (body scan), sitting and walking meditation, yoga exercises and short mindfulness exercises focusing on breathing (Segal et al., 2013, p. 184 ff). Additionally, participants should train mindfulness every day at home and learn to be mindful in their everyday life bringing their attention to the present moment (Segal et al., 2013, p. 246). Mindfulness treatment programs have shown their efficacy in multiple clinical studies pointing to enhanced emotion regulation skills after treatment of several psychiatric disorders (Fjorback, Arendt, Ørnbøl, Fink, & Walach, 2011; Khoury et al., 2013; Linehan, 1993; Segal, Williams, & Teasdale, 2002), as well as improvements regarding physical illnesses, for example reduction of high blood pressure or skin clearing in psoriasis (Kabat-Zinn et al., 1998; van Aalderen et al., 2012).

1.5. Neurobiological correlates of mindfulness

Neurobiological research has investigated different aspects of mindfulness with highly varying study designs. Some studies investigated groups differing in their amount of experience with mindfulness training, ranging from no experience to expert meditators (Farb et al., 2007; Ives-Deliperi, Solms, & Meintjes, 2011; Tang et al., 2007). Various clinical samples with psychiatric as well as psychosomatic disabilities were examined compared to healthy controls (Kabat-Zinn et al., 1998; Williams et al., 2008). Additionally, some studies investigated the neural correlates of mindful states induced by different meditation practices (Hölzel et al., 2007), whereas others examined mindfulness in the confrontation to emotionally arousing stimuli or specific cognitive tasks (Allen et al., 2012; Farb et al., 2010).

Results on expert meditators point to a distinct activation pattern depending on the level of expertise and on the conceptualization the latter. Expert meditators with years of experience and two hours practice daily showed increased rostral anterior cingulate and dorsomedial prefrontal activation during Vipanassa meditation, which the authors link to increased processing of distracting events and more intensive emotion processing (Hölzel et al., 2007). However, a link to well-being was not clearly provided.

The role of prefrontal areas was further supported by (Hasenkamp, Wilson-Mendenhall, Duncan, & Barsalou, 2012), with increased engagement during the focus on mindfulness in meditation experts. Recent reviews underpinned those findings and broadened it to other forms of meditation such as Christian prayers (Cahn & Polich, 2006) and also pointed out the role of increased activation in the anterior cingulate cortex (Chiesa & Serretti, 2010).

The above stated results were partly supported by another review (Tang et al., 2007) with respect to the role of the ACC showing increased activation in expert meditators.

Tang and colleagues concluded that the activation in prefrontal regions is mediated by meditation experience with reduced activation in expert meditators. Nevertheless, it has to be critically taken into account that Tang and colleagues use the effort level to achieve a meditative state as the variable for labelling experts. In their approach, they put the results from Hölzel and colleagues (2007) as medium even though they themselves critically comment that these studies did not collect information on effort. Furthermore, Tang and colleagues did not include another study on mindful meditation with healthy subjects who participated in an MBSR course and had at least four years of mindfulness experience, which pointed to increased activation cortical midline and right posterior cingulate cortex (Ives-Deliperi et al., 2011).

Leaving the concept of effort behind, studies in healthy participants after eight weeks MBSR training revealed decreased VMPFC and DMPFC activity and increased recruitment of viscerosensitive networks and lateral prefrontal areas in a mindfulness-similar task (Farb et al., 2007). Further studies have explored the effect of mindfulness training on distinct tasks, for example sadness provocation and response inhibition, pointing to increased recruitment of viscerosensitive networks and dorsolateral, ventrolateral and superior prefrontal areas (Allen et al., 2012; Farb et al., 2010), supporting the previously cited findings. In a clinical population, the effectiveness of MBSR was associated with increased activation in posterior parietal attention-related brain regions pointing to greater attentional engagement (Goldin, Ziv, Jazaieri, Hahn, & Gross, 2013). Short mindfulness-related interventions like affect-labelling and focused-breathing with untrained subjects point towards increased activation from attention networks including the DMPFC, dACC and the insula (Dickenson et al., 2013). Furthermore, trained as well as untrained subjects showed reduced amygdala activation and increased prefrontal activation (Burklund et al., 2014; Creswell et al., 2007; Herwig et al., 2010; Lieberman et al., 2007).

It becomes obvious, that the investigation of the concept of mindfulness is still in a fledgling stage. Due to the large differences in study designs, the results reported so far resemble small parts of a large puzzle with some areas already becoming clearer but others being still separated and little understood.

1.6. Aims of the studies

The presented studies, as part of a large research project on emotion regulation, intended to clarify the neural correlates of different emotion regulation strategies and self-reflection processes in healthy participants and patients with depressive disorders. The first study builds upon a previous work of our research group (Herwig et al., 2010) on neural correlates of self-reflection and emotion introspection in healthy subjects. This previous study revealed that emotion-introspection, similar to a short mindfulness intervention, causes a down-regulation of the amygdala associated with reduced emotional arousal. Emotion introspection can be regarded as a very basic part of mindfulness, instructing the subject to be aware of current emotions and bodily feelings. It contains central components of the definition of mindfulness (Kabat-Zinn, 2003). However not all components and especially the term mindfulness is not mentioned.

The presented study investigated the neural correlates of self-reflection and emotion-introspection in acutely and remitted depressed patients. The comparison of the neural mechanisms in acutely depressed and remitted patients might contribute to the identification of the mechanisms of remission and the persisting neural differences that increase the risk for relapse. It is additionally be helpful to evaluate the effectiveness of psychotherapeutic interventions for patients in the different states of a depression. In this study, we chose a short sequence of emotion introspection compared to self-reflection without the confrontation with emotionally arousing stimuli. The emotion introspection can be compared to a short mindfulness intervention. We assumed to gain insight in how far mindfulness, even without any prior training, can be applied in such a basic paradigm.

The second study used a paradigm with emotionally arousing stimuli in a healthy sample, aiming for the comparison of the neural basis of two different approaches of dealing with these stimuli, namely mindfulness and cognitive control. This study extends prior neurobiological research on mindfulness in healthy novices, as their ability to apply mindfulness under emotionally arousing circumstances is examined.

Taken together, these studies aimed for extending the knowledge about the neurofunctional mechanisms of mindfulness. We investigated the ability of different groups of people to perform mindfulness-related interventions, based on the hypothesis that they are connected with specific neural correlates, for instance the down-regulation of the amygdala (Herwig et al., 2010). Furthermore, differences in neural correlates of mindful states in confrontation with emotionally arousing stimuli and on the other hand “pure” mindful states without any confrontation are in the focus. Given that research on mindfulness interventions has hardly just begun, this thesis provides some puzzle pieces that might be helpful for getting the bigger picture about mindfulness within the course of the next years.

2. Methods: functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroscience technique that has become highly important in clinical diagnostic and neuroscience research in the diverse fields of interest. FMRI uses the blood oxygenation level dependent (BOLD) response. The BOLD response is based on the magnetic state of haemoglobin that changes depending on its oxygenation (Uludag, Dubowitz, & Buxton, 2006). Oxygenated haemoglobin is diamagnetic, whereas deoxygenated haemoglobin is paramagnetic. Deoxygenated haemoglobin disturbs the MR-signal, whereas the signal increases when the concentration of deoxygenated haemoglobin is reduced.

Neural activation is associated with increased local blood flow plus an increase in oxygenated haemoglobin. As a consequence, the concentration of deoxygenated haemoglobin is reduced and the signal increases.

The clear advantage of fMRI in comparison to other methods such as Electroencephalography (EEG) lies in the high resolution of the obtained images that provide a basis for a precise localization of the activated area. The disadvantage of the BOLD-response is, that it is relatively slow with its maximum at 4-8 s after the initiation of the neural activation (Jäncke, 2013) Therefore the technique is restricted to slow neural events, as fast processes would be difficult to identify due to the overlapping of their fMRI-signals.

3. Original Research Articles

3.1. Study 1: Changes in the neural networks of self-reflection and emotion introspection with remission of depression – a longitudinal study

Sarah Opialla*[a,e], Uwe Herwig[a,b], Sigrid Scherpiet[a,e], Anna Hittmeyer[a], Katja Cattapan[c,d], Lutz Jäncke[e], Annette Brühl[a,f]

[a] Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry Zurich, Zurich, Switzerland

[b] Department of Psychiatry and Psychotherapy III, University of Ulm, Ulm, Germany

[c] Sanatorium Kilchberg, Psychiatric Clinic, Kilchberg, Switzerland

[d] University Hospital of Psychiatry, University of Bern, Bern, Switzerland

[e] Psychology Department, Department of Neuropsychology, University of Zurich, Zurich, Switzerland

[f] Department of Psychiatry and Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK

Corresponding author:
Sarah Opialla
University Hospital of Psychiatry Zurich
Department of Psychiatry, Psychotherapy and Psychosomatic
Militärstrasse 8, Postfach 1930
8021 Zurich, Switzerland
Fax: +41(0)44 296 74 09
Phone: +41(0)44 296 73 62
E-Mail: sarah.opialla@puk.zh.ch

Submitted for Publication in Psychiatry Research: Neuroimaging

Abstract

The ability to regulate emotions and reflect on oneself is hindered in depressive disorders. The study of patients in an acutely depressed state and in remission could help to contribute to an enhanced understanding of changes underlying the remission and identifying trait or scar-like correlates of depression.

We investigated 8 patients while being in acute depression as well as in remission by means of functional magnetic resonance imaging during cognitive self-reflection, emotion introspection and during a neutral condition. We also compared the remitted patients to 8 matched healthy control participants performing the same task.

Comparing acute and remitted depression resulted in distinct activation patterns of self-reflection and emotion introspection. In both states, emotion introspection was associated with reduced amygdala and VMPFC activation. In addition, middle/inferior temporal cortex was less active during emotion introspection in the remitted state. In remission, self-reflection increased activations of the DLPFC and middle/inferior temporal areas, whereas the depressed state was characterized by increased activation in the right amygdala and left cuneus. This could reflect more automated rumination in acute depression, potentially replaced by a more controlled reflection process after remission.

Keywords: mindfulness, fMRI, emotion regulation, MDD

1. Introduction

The Global Burden of Disease Study 2010 qualified major depressive disorder (MDD) as a leading cause of burden worldwide (Ferrari et al., 2013). According to Beck's cognitive model, depression is characterized by distorted automatic thoughts, dysfunctional beliefs and information-processing biases (Beck, 1979; Beck, 2008). Psychological therapies address these distortions, for example by revising negative self-schemata as part of cognitive behaviour therapy (CBT; Beck et al., 1979) or by training to disengage from ruminative self-focus using mindful self-awareness as taught in mindfulness-based cognitive therapy (MBCT; Segal et al., 2013). Nevertheless, little is known about the distinct neural mechanisms underlying these strategies and – specifically – in how far a clinical improvement in depressive symptoms results in a normalization of neurofunctional patterns or at least an increased similarity to healthy subjects. On the other hand, persistent changes after remission of depressed symptoms could represent either scar-like changes or pre-existing traits possibly reflecting vulnerability (Ormel et al., 2013).

Short mindfulness interventions in meditation-naïve healthy subjects in prior studies activated parietal and prefrontal structures (e.g. dorsomedial prefrontal cortex (DMFPC), dorsal anterior cingulate cortex (dACC)) as well as the insula (Dickenson et al., 2013), amygdala and parahippocampal gyrus (Lutz et al., 2014).

Emotion labelling, which could be regarded as a minimal mindfulness intervention, was associated with reduced amygdala activity and increased activation in medial and ventrolateral prefrontal cortex (Lieberman et al., 2007), parallel to an own study on mindful awareness of one's own feelings (Herwig et al., 2010).

Ruminative self-focus in depression has been associated with increased activations in limbic, medial prefrontal (MPFC) and dorsolateral prefrontal (DLPFC) areas (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010). While distraction and mindful self-focus were associated with positive effects on mood, ruminative self-focus even intensified depressed mood (Huffziger & Kuehner, 2009). Additionally, self-focus in depression was found to be associated with increased activations in medial prefrontal regions (reviews: Lemogne et al., 2012; Northoff, 2007).

In the present study, we aimed to investigate the changes in brain activation associated with the remission of a major depressive episode in patients with MDD. We combined the investigation of two core features of sustained psychological well-being in MDD – namely self-reflection and emotion introspection – and its change in the course of remission and in comparison to a healthy state. This comparison might help to gain insight into the remission process, identifying vulnerability factors for relapse and common and distinct neural correlates of these two mental states (depressed/remitted). As emotions in everyday life often arise without explicit external triggers, and successful emotion regulation starts with the awareness of one's emotions, may they be externally or internally generated, we did not confront participants with emotional stimuli (Herwig et al., 2010).

Until now, there is no comparable data on short interventions in remitted or acutely depressed patients. However, the effectiveness of MBCT in reducing depressive symptoms (van Aalderen et al., 2012) and improving emotion regulation skills (Britton, Shahar, Szepsenwol, & Jacobs, 2012) lead us to hypothesize that patients in remission will show reduced activations of the amygdala during emotion introspection compared to self-reflection such as had been observed in healthy subjects (Herwig et al., 2010).

In parallel, we hypothesized that increased amygdala activity during self-reflection in acutely depressed patients is reduced with successful treatment, assuming an underlying rumination process in acute depression that is reduced with remission of depression. Finally, we expected that increased VMPFC, DMPFC and DLPFC activation in the acutely depressed patients during self-reflection is reduced with successful treatment, corresponding to a reduced self-focus.

2. Methods

2.1. Subjects

Nine subjects (age 31-53, M = 40.22, SD = 8.17, 5 females, all right-handed) with remitted depression participated in the present study. These subjects are a subsample out of 30 patients who had participated in a former study (Herwig, Opialla, Cattapan, Jäncke, & Brühl, 2014), who at the initial recruitment had fulfilled the criteria for a diagnosis of mild to moderately severe major depression, assessed according to ICD-10 and DSM-IV criteria by a trained psychiatrist. For the current study, participants were contacted via telephone and were asked to participate in a follow-up study. If they agreed, the participants underwent a telephone screening to exclude patients with acute major depression. Of the 30 subjects who participated in the first study, 25 could be reached by phone. Thirteen were not interested in participating again, three were (still or again) acutely depressed and nine were willing to participate. Besides acute depression, further exclusion criteria were excessive consumption of alcohol, nicotine, or caffeine, benzodiazepines, neuroleptics, psychiatric axis I comorbidities assessed with the German version of the Mini-International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998), neurological disorders and contra-indications against magnetic resonance imaging (MRI) examinations, as assessed by a semi-structured interview.

Additionally to a within-subject analysis, the remitted patients were compared to a control group of age- and gender-matched healthy subjects of a former study (for details, Herwig et al., 2010). All subjects gave written informed consent and received a financial compensation. The local ethics committee had approved all parts of the study (initial and follow-up recruitment). The study was performed in accordance with the Declaration of Helsinki ("World Medical Association, Declaration of Helsinki," 2002).

2.2. Questionnaires

Participants completed German versions of two self-report questionnaires assessing depression (Self-Rating Depression Scale, SDS; Zung, 1965) and Beck's Depression Inventory (BDI; Beck et al., 1961) and trait mindfulness (Mindfulness Attention and Awareness Scale, MAAS; Brown & Ryan, 2003; Freiburg Mindfulness Inventory, FMI; Walach, Buchheld, Buttenmüller, Kleinknecht, & Schmidt, 2006). Furthermore, depression was assessed with the Hamilton Depression Scale (HAM-D 21 item version; Hamilton, 1960) and the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979).

Statistical analyses of the scales were performed with the Statistical Package for the Social Sciences (SPSS), version 21, using paired and independent student's t-tests, $\chi 2$-tests and Pearson's product-moment correlation on a statistical significance level $P < 0.05$.

2.3. FMRI acquisition

Imaging was performed on a General Electric 3.0 T Signal^{TM} HD Scanner equipped with an 8-channel head coil (GE Medical Systems, Milwaukee, USA). Across a single functional run, 584 functional volumes were obtained covering 22 sequential axial slices covering the whole brain (repetition/echo time (TR/TE) 1980/32ms, slice thickness 3.5 mm with 1 mm gap, resulting voxel size 3.125 x 3.125 x 4.5 mm, field of view 200 mm, flip angle 70°). Four dummy scans were performed to allow for T1* equilibration effects. T2-weighted functional magnetic resonance images were obtained to exclude possible T2-sensitive brain abnormalities. High resolution 3D T1 weighted anatomical volumes were acquired for co-registration with functional data (TR/TE 9.2/2.1; 1x1x1 mm^3 resolution, axial orientation, 176 slices).

2.4. Experimental task

Prior to scanning, all subjects performed a short training session to get accustomed to the task and the type of stimuli. The task was previously designed and carried out with a sample of participants without psychiatric diagnosis (Herwig et al., 2010). It consisted of three conditions that were presented in pseudo-randomized order during functional Magnetic Resonance Imaging (fMRI). The conditions were cognitive self-reflection (“think”), emotion-introspection (“feel”) and a neutral condition (“neutral”). In the “think” conditions, subjects were instructed as follows: “Think of yourself, reflect who you are, about your goals, etc.”. In the “feel” condition, the instruction was: “Feel yourself, be aware about your current emotions and bodily feelings” and in the neutral condition: “Do nothing specific, just await the neutral picture”. The cues were intuitively understandable and used only few cognitive resources. Furthermore, the task did not require any motor reaction that could have interfered with the participants’ performance.

A cue (1000ms) indicated the following condition (10880 ms) and a neutral picture (3960 ms/ 2TR; TR repetition time for the fMRI volumes) served as a distraction and end of the condition period (Figure 1). A baseline period of 15840 ms/ 8 TR followed before the next trial started. The cue and the condition together were 11880 ms/ 6 TRs. Each subject performed 12 trials of each condition in a pseudorandomized order. The task was programmed with Presentation™ (Neurobehavioral Systems, USA). The stimuli were presented via digital video goggles (Resonance Technologies, Northridge, CA).

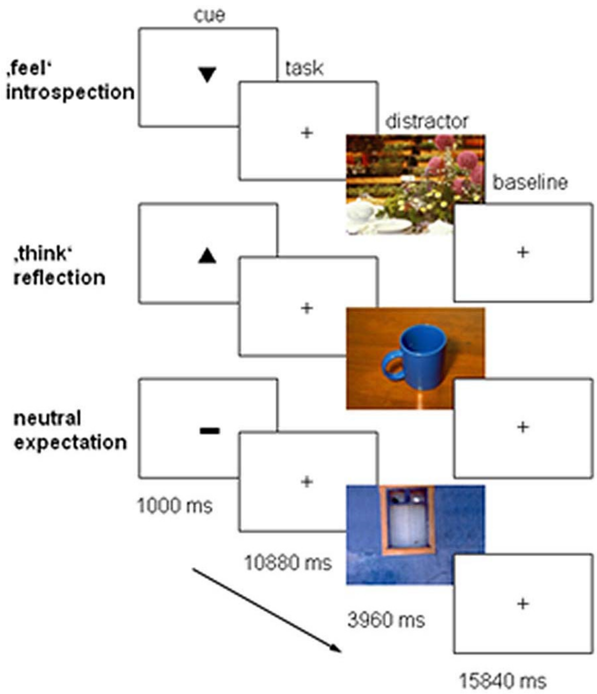

Figure 1 Experimental task. Three conditions were cued: mindfulness-comparable emotion introspection 'feel' (awareness of actual emotions), cognitive self-reflection 'think' ("who am I…"), and a neutral period. Neutral pictures served as a distractor and indicated the end of the condition. Durations are indicated in milliseconds.

2.5. FMRI data analysis and statistics

FMRI Data were analysed using BrainVoyager QX 2.6 (Brain Innovation, Maastricht, The Netherlands, (Goebel, Esposito, & Formisano, 2006). The functional data were pre-processed to maximize signal-to-noise contrast. Pre-processing included motion correction, slice scan time correction, high frequency temporal filtering and linear detrending. To improve the data quality, an intensity inhomogeneity correction was carried out on the anatomical data sets. Functional images were superimposed on the 2D anatomical images and incorporated into 3D data sets. Each data set was normalized and converted to Talairach space (Talairach & Tournoux, 1988), resulting in a voxel size of 3x3x3 mm^3, followed by spatial smoothing with an 8mm Gaussian kernel for subsequent group analysis. The design matrix consisted of the two within subject-factors “time” and “condition”. The factor “time” described the session number regarding the first and the second scan (2 levels). The factor “condition” consisted of the three conditions “think”, “feel” and “neutral” (3 levels). Single run design matrices (SDMs) were defined for every functional run including motion confounds. Due to the small sample size, we calculated whole-brain fixed effects analyses with separate subject predictors for the three contrasts of interest “(feel^{acute} > neutral^{acute}) > (feel^{remi} > neutral^{remi})”, “(think^{acute} > neutral^{acute}) > (think^{remi} > neutral^{remi})” and “(feel^{acute} > think^{acute}) > (feel^{remi} > think^{remi})”.

Furthermore, a region-of-interest (ROI) analysis with predefined cubic anatomic ROIs was carried out for each contrast of interest. The ROIs were defined according to previous studies (amygdala: Costafreda, Brammer, David, & Fu, C. H. Y., 2008; DMPFC, VLPFC, VMPFC: Creswell et al., 2007; DLPFC: Herwig et al., 2010) and anatomically validated using Talairach client (Lancaster et al., 2000). ROI coordinates and sizes are given in Table 3 and 5.

For each ROI, the mean beta-weights for the three contrasts were compared in the acute and the remitted depressed state. Furthermore, a group comparison between the now remitted, formerly depressed group and the matched healthy participants’ group was calculated. We used paired and independent student’s t-tests (depending on the comparison) using a statistical threshold of $P < 0.05$ and calculated effect sizes using Cohen’s d (Cohen, 1988). Additionally, we investigated the activity in the primary visual cortex (V1) during picture perception to control for possible general perceptual and attentional differences.

Moreover, we compared whole-brain activation in the contrasts of interest between the remitted group and the healthy control group, calculating a random effects analysis. We used a voxel-wise statistical level of $P < 0.001$. A Monte-Carlo-Correction (Goebel et al., 2006) was applied to avoid alpha-error-accumulation, yielding a corrected cluster-level of $P < 0.05$.

3. Results

3.1. Participants

The final analysis included eight remitted patients (ages 31-53, M = 39.00, SD = 7.80, all right-handed, 4 female), as one patient had to be excluded later due to severe fMRI artefacts (head movements with more than 3 mm in translation and/or rotation).

The remitted patient group and the healthy control group did not differ significantly regarding age (t (14) = 1.36, P = 0.20), and sex was equally distributed. One subject of the acutely depressed sample did not complete the MAAS.

The depression ratings (SDS, BDI, HAM-D, MADRS) revealed clinically relevant degrees of depression in the acutely depressed state and significantly lower scores in the remitted state (Table 1). Remission criteria were a score of < 11/63 points in BDI, < 15/67 points in HAM-D or < 10/60 in MADRS (at least two criteria fulfilled) and were fulfilled by all included patients. Trait mindfulness (FMI, MAAS) did not change due to successful treatment of depression, confirming trait-like characteristics of these questionnaires.

Table 1

Psychometric measures of included subjects per group

Scale	RD	AD	HC	Independent t-test		Paired t-test	
	M (*SD, N*)	*M* (*SD, N*)	*M* (*SD, N*)	RD-HC		RD-AD	
				t	*P* (*d*)	*t*	*P* (*d*)
SDS	44.69(6.19,8)	66.25(6.75,8)	32.97(4.91, 8)	4.19	0.001***(2.24)	8.31	0.000*** (6.28)
MAAS	60.00(9.52,7)	54.00(9.04,7)	69.38(9.88,8)	-1.86	0.085	-1.52	0.188
FMI	37.57(7.35,7)	31.88(3.18,8)	42.25(3.37,8)	-1.62	0.129	-2.27	0.064
HAMD	4.25(3.45,8)	22.88(7.49,8)				7.39	0.000*** (5.59)
MADRS	5.25(3.41,8)	25.25(6.76,8)				7.54	0.000*** (5.70)
BDI	9.00(6.07,8)	24.38(9.01,8)				3.69	0.188

Significant differences are marked with * ($P \leq 0.05$), ** ($P \leq 0.01$) and *** ($P \leq 0.001$). Effect sizes (d) are indicated in brackets and are given for significant results only. Abbreviations: RD Remitted Depressed Group, AD Acutely Depressed Group, HC Healthy Control Group, M Mean, SD Standard Deviation, N sample size, SDS Self-rating Depression Scale, MAAS Mindful Attention Awareness Scale, FMI Freiburg Mindfulness Inventory, HAMD Hamilton Depression Scale, MADRS Montgomery-Åsberg Depression Rating Scale, BDI Beck Depression Inventory.

The comparison of remitted patients and healthy controls revealed a significantly higher depression score (SDS), whereas mindfulness scores were not different between the groups. The duration between the first and the second scan ranged from 126 to 884 days (*M* = 384.38, *SD* = 228.50). For an overview of the medication in the acute depression and remitted state, please refer to supplementary material, Table S1.

3.2. FMRI Analysis: acute versus remitted depressed state

The whole-brain within-subject comparison for patients in the acutely depressed compared to the remitted state revealed significant differences for the contrast “feel > think” (Table 2).

Table 2

Whole brain comparison acutely depressed versus remitted depressed patients

Anatomic region	Brodmann area	Cluster size mm^3	Peak Talairach Coordinates			*t*-max	*P*-max
			x	*y*	*z*		
(feel > think)AD > (feel > think) RD							
MidTG R	21	549	59	-26	-3	-3.964602	0.000074
Cuneus L	17	788	2	-95	12	4.445455	0.000009
ITG L, MidTG L	20, 21	909	-55	-26	-15	-4.029194	0.000056

Activated areas in a fixed effects analysis (ffx) with a voxel-wise threshold of $P < .001$ of the contrast remitted depressed > acutely depressed. Minimum cluster size (for cluster-wise threshold of $P < 0.05$, Monte-Carlo corrected) 465 mm^3 (18 functional voxel). Abbreviations:, MidTG Middle Temporal Gyrus, ITG Inferior Temporal Gyrus, R Right, L Left, AD acute depressive patients, RD remitted depressive patients.

It revealed an opposite effect for the acutely depressed and the remitted state in the right middle temporal gyrus (Figure 2A): While depressed, the patients showed increased activations during emotion introspection and decreased activations during self-reflection, whereas in remission, the patients showed decreased activations during emotion introspection and increased activations during self-reflection and overall stronger effects. In the left middle temporal gyrus and inferior temporal gyrus, we found a similar pattern with more pronounced differences in the remitted state, showing decreased activations during emotion introspection and increased activations during self-reflection (Figure 2B).

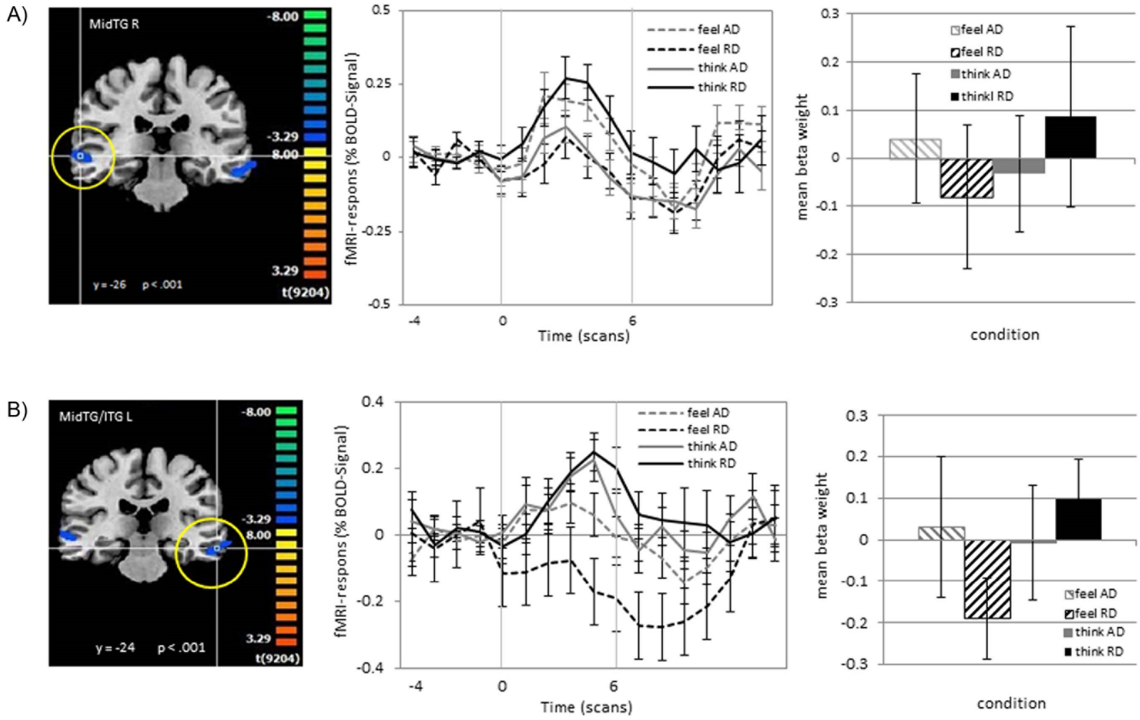

Figure 2 A and B Results of contrast ‘feel’ > ‘think’ for the comparison acute > remitted depressed state. Reduced brain activity in the right MidTG and left MidTG/ITG in the remitted depressed state (P < 0.001 voxel-wise, P <0.05 cluster-wise). Average time course: task-period between the two grey bars. Error bars indicate standard error. Abbreviations: L left, R right, MidTG Middle Temporal Gyrus, ITG Inferior Temporal Gyrus, feel = emotion introspection, think = self-reflection.

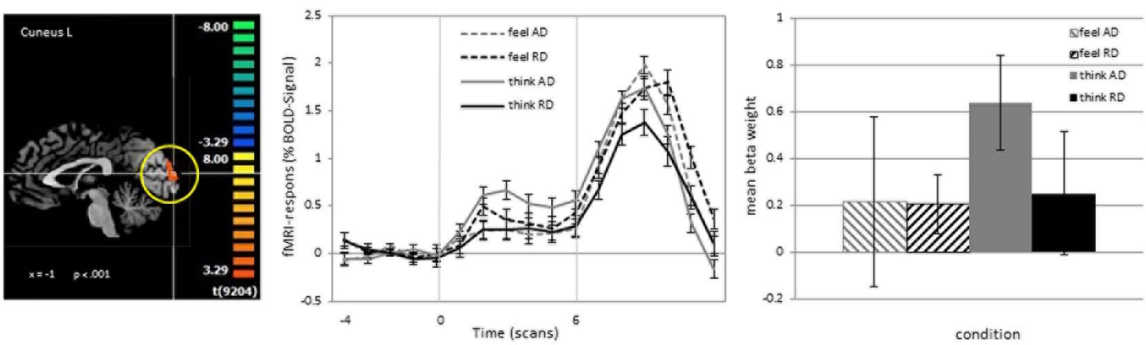

Figure 3 Results of contrast ‘feel’ > ‘think’ for the comparison acute > remitted depressed state. Increased brain activity in the Cuneus in the remitted depressed state (P < 0.001 voxel-wise, P <0 .05 cluster-wise). Average time course: task-period between the two grey bars. Error bars indicate standard error. Abbreviations: L Left, feel = emotion introspection, think = self-reflection.

In the depressed state, the differences were less distinct and in the opposite direction. Furthermore, we found increased activations in the left cuneus during self-reflection compared to emotion introspection in the depressed state, whereas these conditions differed little in the remitted state (Figure 3).

The ROI-analysis revealed significant differences in the right amygdala for the contrast “feel > think”, with a stronger down-regulation of the amygdala during emotion introspection compared to self-reflection in acute depression compared to remission. Furthermore, the left and right VMPFC and right DLPFC ROIs showed significantly larger activation differences in the contrast “feel > think” in the remitted compared to the acutely depressed state. In the VMPFC, this result seems to driven by a reduced recruitment during emotion introspection (“feel”) after successful treatment, whereas in the DLPFC the results showed a strong increase of activation during self-reflection (“think”) in the remitted state. For details on the ROI-Analysis refer to Table 3.

Table 3

ROI analysis of acutely depressed compared to remitted depressed patients

ROI Coordinates $x / y / z$	Cluster size mm^3	(Feel > Think) $_{acute}$ > (Feel > Think) $_{remi}$		(Feel > neutral) $_{acute}$ > (feel > neutral) $_{remi}$		(Think > neutral) $_{acute}$ > (think > neutral) $_{remi}$	
		t	*P* (*d*)	*t*	*P* (*d*)	*t*	*P* (*d*)
Amygdala R 22/-6/-12	729	-2.155	0.0311* (1.63)	1.020	0.3079	3.183	0.0015** (2.41)
Amygdala L -22/-6/-12	729	-1.396	.1629	1.112	0.2662	2.516	0.0119* (1.90)
VMPFC R 7 / 57 / 23	3375	2.596	0.0095** (1.96)	3.825	0.0001*** (2.89)	1.263	0.2064
VMPFC L -7/57/23	3375	2.519	0.0118* (1.90)	4.165	0.0000*** (3.15)	1.682	0.0925
V1 R 5 / -86 / -3	729	-0.473	0.6360	1.308	0.1908	1.792	0.0731
V1 L - 5 / -86 / -3	729	-0.549	0.5827	0.941	0.3468	1.498	0.1342
DMPFC R 6/6/50	1728	0.534	0.5929	1.634	0.1023	1.114	0.2654
DMFPC L -6/6/50	1728	0.710	0.4780	0.154	0.8776	-0.554	0.5796
DLPFC R 35/20/28	3375	2.308	0.0210* (1.75)	2.362	0.0182* (1.79)	0.075	0.9408
DLPFC L -35/20/28	3375	-0.017	0.9812	0.703	0.4819	0.726	0.4678
VLPFC R 38/32/2	3375	0.020	0.9812	- 0.277	0.7818	-0.299	0.7649

VLPFC L -38/32/2	3375	0.287	0.7743	0.070	0.9438	-0.217	0.8285

ROI analysis of *emotion introspection versus self reflection in acutely versus remitted depressed patients* ((Feel > Think) acute > (Feel > Think) remitted), *emotion introspection in acutely versus remitted depressed patients* (Feel acute > Feel remitted) and *self reflection in acutely versus remitted depressed patients* (Think acute > Think remitted). Significant differences are marked with * (*P* ≤ 0.05), ** (*P* ≤ 0.01) and *** (*P* ≤ 0.001). Effect sizes (d) are indicated in brackets and given for significant results only.

Abbreviations: V1 primary visual cortex, VMPFC ventromedial prefrontal cortex, DMPFC dorsal medial prefrontal cortex, VLPFC ventrolateral prefrontal cortex, DLPFC dorsolateral prefrontal cortex, R right, L left.

3.3. FMRI-Analysis: remitted patients versus health controls

The whole-brain group comparison between the remitted patients and the control group revealed no significant differences for all investigated contrasts. The ROI-Analysis showed a decreased left VMPFC contrast difference for the comparison "feel > think" in healthy controls. For details on the ROI-Analysis refer to Table 4.

Table 4

ROI analysis of remitted depressed patients compared to healthy control subjects

ROI Coordinates *x / y / z*	Cluster size mm^3	Feel > Think		Feel > neutral		Think > neutral	
		t	*P* (*d*)	*t*	*P* (*d*)	*t*	*P* (*d*)
Amygdala R 22/-6/-12	729	-.383	0.7072	-1.903	0.0778	-2.122	0.0521
Amygdala L -22/-6/-12	729	-.144	0.8880	-2.114	0.0529	-.1654	0.1203
VMPFC R 7 / 57 / 23	3375	-1.442	0.1714	-0.889	0.3893	0.962	0.3525
VMPFC L -7/57/23	3375	-2.324	0.0357* (-1.242)	-1.952	0.0713	0.913	0.3767
V1 R 5 / -86 / -3	729	-1.372	0.1915	-0.583	0.5691	0.706	0.4920
V1 L - 5 / -86 / -3	729	-0.435	0.6703	-0.3990	0.7022	0.197	0.8465
DMPFC R 6/6/50	1728	-1.246	0.2334	-0.240	0.8139	0.606	0.5542

DMFPC L -6/6/50	1728	1.169	0.2620	-1.154	0.2680	-2.039	0.0608
DLPFC R 35/20/28	3375	-1.887	0.0801	-1.914	0.076	0.663	0.5184
DLPFC L -35/20/28	3375	-1.402	0.1827	-0.554	0.5881	0.887	0.390
VLPFC R 38/32/2	3375	-1.173	0.2603	1.260	0.2282	1.891	0.0796
VLPFC L -38/32/2	3375	-0.793	0.4410	0.596	0.5606	1.012	0.3285

ROI analysis of emotion introspection versus self reflection (Feel > think), emotion introspection versus neutral expectation (Feel > neutral) and self reflection versus neutral expectation (Think > neutral) in healthy control subjects versus remitted depressive patients. Significant differences are marked with * ($P \leq 0.05$), ** ($P \leq 0.01$) and *** ($P \leq 0.001$). Effect sizes (d) are indicated in brackets and are given for significant results only. Abbreviations: V1 primary visual cortex, VMPFC ventromedial prefrontal cortex, DMPFC dorsal medial prefrontal cortex, VLPFC ventrolateral prefrontal cortex, DLPFC dorsolateral prefrontal cortex, R right, L left.

4. Discussion

We investigated the differential activations of self-reflection and emotion introspection in patients with acute and remitted depression using a longitudinal within-subject design. We found reduced amygdala and VMPFC activation during introspection in both states, decreased bilateral middle and inferior temporal gyrus activations in emotion introspection and increased activations in self-reflection in remission and a reversed, weaker effect in the acutely depressed state.

In line with our results, increased activations in the left middle temporal gyrus have been found for a narrative self-focus compared to a mindfulness-like condition in a healthy sample, interpreted along with increased inferior lateral prefrontal and angular gyri activations as part of the linguistic semantic network (Farb et al., 2007). However, findings supporting an involvement of inferior and middle temporal areas in self-reflection and emotion introspection are rare. Nevertheless, the literature points to an involvement of this region in semantic control and semantic processing (Whitney, Kirk, O'Sullivan, Lambon Ralph, M. A., & Jefferies, 2011; Visser & Lambon Ralph, M. A., 2011). Due to the lack of further supporting evidence, this finding in our study cannot be easily explained. One possible interpretation could be an increased ability to consciously engage in a – potentially verbal - reflection process after successful treatment, and additionally possibly a more detached, more passive « watching » emotion introspection process.

Additionally, we found less activation in the cuneus during self-reflection after successful treatment in comparison to the acutely depressed state. The cuneus is known to be involved in basic visual processing (Vanni, Tanskanen, Seppa, Uutela, & Hari, 2001), but has also been linked to ruminative processes in depression (Cooney et al., 2010). Thus, this finding might correspond to reduced imagery during self-focus in the remitted state.

The ROI-analysis of the amygdala revealed strongly decreased activation during emotion introspection compared to self-reflection in both the acutely depressed and remitted state, suggesting that both states go along with the ability to regulate ones amygdala activity with a mindfulness-close approach. This finding is consistent with prior studies on mindful awareness in novices and affect labelling (Herwig et al., 2010; Lieberman et al., 2007; Creswell et al., 2007). However, it was unexpected that the acute depressed state was associated with a stronger down-regulation of the amygdala during emotion introspection. One possible explanation for this finding, however hypothetical at the current point, could be a higher baseline amygdala activity in the depressed state which resolves with successful treatment (e.g. Delaveau et al., 2011).

This hypothetical interpretation would be supported by reduced bilateral amygdala activation during self-reflection in remission. While increased amygdala activation in acute depression might arise from emotional arousal induced by the heightened self-focus (Cooney et al., 2010), remission might enable patients to keep up a more reflective engagement. In line with our hypothesis and with previous research (Cooney et al., 2010; Lemogne et al., 2012), there was a trend towards less VMPFC activation during self-reflection after successful treatment compared to the acutely depressed state, which might also be related to reduced self-focus.

The more prominent and rather unexpected result was a strong decrease in bilateral VMPFC activations during emotion introspection compared to self-reflection in both, depressed and remitted state, with larger effects in remission. Previous research in healthy subjects has pointed to successful emotion regulation through an MPFC influence on the amygdala activation by mindfulness-close interventions (Herwig et al., 2010); Creswell et al., 2007). However, there is data supporting a down-regulation of the VMPFC for mindful states, as found for trained mindfulness practitioners (Farb et al., 2007; Taylor et al., 2011). Our results expand those findings, pointing to the ability of even untrained subjects to down-regulate their VMPFC activation by mindfulness.

The stronger activation decrease after successful treatment might thus reflect the improved ability to engage in mindfulness.

Compared to healthy controls, we found increased left VMPFC activation in remitted depression for the contrast “feel > think”, mainly resulting from a less reduced activation during emotion introspection in the remitted sample. This result points to some persisting difference in the ability to engage in mindful emotion regulation associated with VMPFC down-regulation (Farb et al., 2007; Taylor et al., 2011). Nevertheless, the comparison of remitted depressed patients and healthy controls principally indicates that these groups merely differ in the brain activation during emotion introspection and self-reflection.

In the DLPFC ROI analysis, we found increased activations during self-reflection compared to emotion introspection in the remitted state. The acutely depressed state differed significantly from the remitted state in this contrast and showed hardly any activation differences. An increased DLPFC activation has been associated with ruminative self-focus (Cooney et al., 2010), self-referential processing (review: Lemogne et al., 2012) and increased self-focus in depression (Grimm et al., 2009). Contrary, Lemogne and colleagues (2010) found no changes in DLPFC activation in self-referential processes in depressed patients before and after antidepressant therapy, but an increase of DLPFC activation in a non-self-referential condition after therapy. However, resting state and functional studies reported a DLPFC hypo-activity for depression (Koenigs & Grafman, 2009; Soares & Mann, 1997) and increased DLPFC activation was found during self-reflection in the healthy group investigated by Herwig and colleagues (2010). We therefore assume that the increased DLPFC activation should be seen in the context of remission and a more adaptive and cognitive realization of the instruction to self-reflection, whereas the acutely depressed state is characterized by less reflected rumination and hyper-focusing on the self which fits to the increased amygdala activation.

The most limiting factor in our study is the small sample size. Therefore, all results have to be interpreted with care and should be replicated in a larger sample.

Nevertheless, our longitudinal approach had the distinct quality that we only included remitted patients in our within-subject-design, whereas other studies mostly measured patients pre and post treatment reporting an improvement of symptoms but not explicitly remission as a criterion for inclusion in the analysis (Yoshimura et al., 2013). The within-subject analysis balances at least some of the limitations due to the low number of overall participants. Further limitations derive from the lack of longitudinal data in the control group and large time period differences between pre and post scan between subjects owing to the remission criterion.

Future studies should continue the investigation of remitted patients and expand the design to emotion regulation and self-reflection under stressful events, such as emotional arousing stimuli. This could shed light on whether the promising effects of mindfulness-close emotion introspection hold out under real-life conditions and following, whether such interventions should be implemented more prominently in psychotherapy.

In summary, our study shows distinct activation patterns of self-reflection and emotion introspection in acute and remitted depression. Self-reflection involved increased activations of the DLPFC and middle/inferior temporal areas after successful treatment pointing to a cognitive reflection process. On the other hand, the acutely depressed state was characterized by increased amygdala und cuneus activation suggesting ruminative processes during self-reflection. Emotion introspection in both states was associated with reduced amygdala and VMPFC activation and the remitted state was additionally associated with decreased middle/inferior temporal activations.

Thus, emotion introspection is accompanied mainly by down-regulation processes in similar areas, whereas self-reflection seems to involve higher order reflection processes in remitted depression contrary to early, more basal activation patterns potentially linked to rumination in acute depression. This points to a trend towards a normalization in brain activation in the course of remission.

Acknowledgment

The study was supported by the Swiss National Foundation No. 320030_146972 and 320030_133009 (UH).

Supplementary Material

Table S1

Overview of the daily medication taken by acute and remitted depressed patients

Patient ID	Acute depressed	Remitted depressed
3	Seroquel 100mg, Remeron 50mg, Seralin*	Seralin 100mg, Lamictal 100mg
12	Trittico 50mg	Deroxat 20mg
17	Effexor 225mg, Crestor 10mg	-
19	Anafranil 112.5mg	Anafranil 75mg
25	Cipralex 15mg, Seroquel 50mg, Trittico 50mg	Cipralex 10mg, Venlafaxine 60mg, Seroquel 12.5mg
26	Cipralex 20mg, Co-Enatec 20mg,Enatec 20mg, Aldactone 25mg	Cipralex 10mg; Dafalgan 60mg, anti-hypertensive medication*
29	Cipralex 20mg, Seroquel XR 50mg, Seroquel 25mg	Cipralex 20mg, Seroquel XR 50mg
30	Efexor 450mg	Irfen if required

*Patient could not give any details on this medication.

References

Beck, A.T., Young, J.E., 1979. Cognitive therapy of depression. Guilford Press, New York.

Beck, A.T., 1979. Cognitive therapy of depression. Guilford Press, New York.

Beck, A.T., 2008. The Evolution of the Cognitive Model of Depression and Its Neurobiological Correlates. American Journal of Psychiatry 165 (8), 969–977. 10.1176/appi.ajp.2008.08050721

Britton, W.B., Shahar, B., Szepsenwol, O., Jacobs, W.J., 2012. Mindfulness-Based Cognitive Therapy Improves Emotional Reactivity to Social Stress: Results from a Randomized Controlled Trial. Behavior Therapy 43 (2), 365–380. 10.1016/j.beth.2011.08.006

Brown, K.W., Ryan, R.M., 2003. The benefits of being present: Mindfulness and its role in psychological well-being. Journal of Personality and Social Psychology 84 (4), 822–848. 10.1037/0022-3514.84.4.822

Cohen, J., 1988. Statistical power analysis for the behavioral sciences, 2nd ed. Lawrence Erlbaum, London.

Cooney, R.E., Joormann, J., Eugène, F., Dennis, E.L., Gotlib, I.H., 2010. Neural correlates of rumination in depression. Cognitive, Affective, & Behavioral Neuroscience 10 (4), 470–478. 10.3758/CABN.10.4.470

Costafreda, S.G., Brammer, M.J., David, A.S., Fu, C. H. Y., 2008. Predictors of amygdala activation during the processing of emotional stimuli: A meta-analysis of 385 PET and fMRI studies. Brain Research Reviews 58 (1), 57–70. 10.1016/j.brainresrev.2007.10.012

Creswell, J.D., Way, B.M., Eisenberger, N.I., Lieberman, M.D., 2007. Neural Correlates of Dispositional Mindfulness During Affect Labeling. Psychosomatic Medicine 69 (6), 560–565. 10.1097/PSY.0b013e3180f6171f

Delaveau, P., Jabourian, M., Lemogne, C., Guionnet, S., Bergouignan, L., Fossati, P., 2011. Brain effects of antidepressants in major depression: A meta-analysis of emotional processing studies. Journal of Affective Disorders 130 (1-2), 66–74. 10.1016/j.jad.2010.09.032

Dickenson, J., Berkman, E.T., Arch, J., Lieberman, M.D., 2013. Neural correlates of focused attention during a brief mindfulness induction. Social Cognitive and Affective Neuroscience 8 (1), 40–47. 10.1093/scan/nss030

Farb, N. A. S., Segal, Z.V., Mayberg, H., Bean, J., McKeon, D., Fatima, Z., Anderson, A.K., 2007. Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. Social Cognitive and Affective Neuroscience 2 (4), 313–322. 10.1093/scan/nsm030

Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J., Vos, T., Whiteford, H.A., Hay, P.J., 2013. Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. PLoS Medicine 10 (11), e1001547. 10.1371/journal.pmed.1001547

Goebel, R., Esposito, F., Formisano, E., 2006. Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: From single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. Human Brain Mapping 27 (5), 392–401. 10.1002/hbm.20249

Grimm, S., Ernst, J., Boesiger, P., Schuepbach, D., Hell, D., Boeker, H., Northoff, G., 2009. Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. Human Brain Mapping 30 (8), 2617–2627. 10.1002/hbm.20693

Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery & Psychiatry (23), 56–62

Herwig, U., Kaffenberger, T., Jäncke, L., Brühl, A.B., 2010. Self-related awareness and emotion regulation. NeuroImage 50 (2), 734–741. 10.1016/j.neuroimage.2009.12. 089

Herwig, U., Opialla, S., Cattapan, K., Jäncke, L., Brühl, A.B., 2014. Discriminative aspects of cognitive self-reflection and mindful introspection in depression. Unpublished manuscript.

Huffziger, S., Kuehner, C., 2009. Rumination, distraction, and mindful self-focus in depressed patients. Behaviour Research and Therapy 47 (3), 224–230. 10.1016/j.brat.2008.12.005

Koenigs, M., Grafman, J., 2009. The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. Behavioural Brain Research 201 (2), 239–243. 10.1016/j.bbr.2009.03.004

Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated Talairach atlas labels for functional brain mapping. Human Brain Mapping 10 (3), 120–131.

Lemogne, C., Delaveau, P., Freton, M., Guionnet, S., Fossati, P., 2012. Medial prefrontal cortex and the self in major depression. Journal of Affective Disorders 136 (1-2), e1–e11. 10.1016/j.jad.2010.11.034

Lemogne, C., Mayberg, H., Bergouignan, L., Volle, E., Delaveau, P., Lehéricy, S., Allilaire, J.-F., Fossati, P., 2010. Self-referential processing and the prefrontal cortex over the course of depression: A pilot study. Journal of Affective Disorders 124 (1-2), 196–201. 10.1016/j.jad.2009.11.003

Lieberman, M.D., Eisenberger, N.I., Crockett, M.J., Tom, S.M., Pfeifer, J.H., Way, B.M., 2007. Putting Feelings Into Words: Affect Labeling Disrupts Amygdala Activity in Response to Affective Stimuli. Psychological Science 18 (5), 421–428. 10.1111/j.1467-9280.2007.01916.x

Lutz, J., Herwig, U., Opialla, S., Hittmeyer, A., Jancke, L., Rufer, M., Grosse Holtforth, M., Bruhl, A.B., 2014. Mindfulness and emotion regulation--an fMRI study. Social Cognitive and Affective Neuroscience (9), 776–785. 10.1093/scan/nst043

Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. The British Journal of Psychiatry 134 (4), 382–389. 10.1192/bjp.134.4.382

Northoff, G., 2007. Psychopathology and pathophysiology of the self in depression — Neuropsychiatric hypothesis. Journal of Affective Disorders 104 (1-3), 1–14. 10.1016/j.jad.2007.02.012

Ormel, J., Jeronimus, B.F., Kotov, R., Riese, H., Bos, E.H., Hankin, B., Rosmalen, J.G., Oldehinkel, A.J., 2013. Neuroticism and common mental disorders: Meaning and utility of a complex relationship. Clinical Psychology Review 33 (5), 686–697. 10.1016/j.cpr.2013.04.003

Segal, Z.V., Williams, J. M. G, Teasdale, J.D., 2013. Mindfulness-based cognitive therapy for depression, 2nd ed. Guilford Press, New York.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International. Neuropsychiatric Interview (M.I.N.I): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry 59 (suppl.20), 22–33.

Soares, J.C., Mann, J.J., 1997. The functional neuroanatomy of mood disorders. Journal of Psychiatric Research 31 (4), 393–432. 10.1016/S0022-3956(97)00016-2

Talairach, J., Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system : an approach to cerebral imaging. Thieme, New York.

Taylor, V.A., Grant, J., Daneault, V., Scavone, G., Breton, E., Roffe-Vidal, S., Courtemanche, J., Lavarenne, A.S., Beauregard, M., 2011. Impact of mindfulness on the neural responses to emotional pictures in experienced and beginner meditators. NeuroImage 57 (4), 1524–1533. 10.1016/j.neuroimage.2011.06.001

van Aalderen, J. R., Donders, A. R. T., Giommi, F., Spinhoven, P., Barendregt, H.P., Speckens, A. E. M., 2012. The efficacy of mindfulness-based cognitive therapy in recurrent depressed patients with and without a current depressive episode: a randomized controlled trial. Psychological Medicine 42 (05), 989–1001. 10.1017/S0033291711002054

Vanni, S., Tanskanen, T., Seppa, M., Uutela, K., Hari, R., 2001. Coinciding early activation of the human primary visual cortex and anteromedial cuneus. Proceedings of the National Academy of Sciences 98 (5), 2776–2780. 10.1073/pnas.041600898

Visser, M., Lambon Ralph, M. A., 2011. Differential Contributions of Bilateral Ventral Anterior Temporal Lobe and Left Anterior Superior Temporal Gyrus to Semantic Processes. Journal of Cognitive Neuroscience 23 (10), 3121–3131. 10.1162/jocn_a_00007

Walach, H., Buchheld, N., Buttenmüller, V., Kleinknecht, N., Schmidt, S., 2006. Measuring mindfulness—the Freiburg Mindfulness Inventory (FMI). Personality and Individual Differences 40 (8), 1543–1555. 10.1016/j.paid.2005.11.025

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., Jefferies, E., 2011. The Neural Organization of Semantic Control: TMS Evidence for a Distributed Network in Left Inferior Frontal and Posterior Middle Temporal Gyrus. Cerebral Cortex 21 (5), 1066–1075

2002. World Medical Association, Declaration of Helsinki: Ethical principles for medical research involving human subjects. Journal of Postgraduate Medicine (48), 206–208.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato, Y., Yoshino, A., Ueda, K., Suzuki, S.-i., Yamawaki, S., 2013. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. Social Cognitive and Affective Neuroscience. 10.1093/scan/nst009

Zung, W.W., 1965. A Self-Rating Depression Scale. Archives of General Psychiatry 12 (1), 63. 10.1001/archpsyc.1965.01720310065008

3.2. Study 2: Neural circuits of emotion regulation: A comparison of mindfulness-based and cognitive reappraisal strategies

Sarah Opialla[1,2], Jacqueline Lutz[1,2], Sigrid Scherpiet[1,2], Anna Hittmeyer[1], Lutz Jäncke[2], Michael Rufer[3], Martin Grosse Holtforth[4,5], Uwe Herwig[1,6], Annette B. Brühl[1,7]

[1] Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, 8023 Zurich, Switzerland

[2] Psychology Department, Department of Neuropsychology, University of Zurich, Binzmühlestrasse 14/25, 8050 Zurich, Switzerland

[3] Department of Psychiatry and Psychotherapy, University Hospital Zurich, Culmannstrasse 8, 8091 Zurich, Switzerland

[4] Psychology Department, Section: Psychotherapy of Affective Disorders, University of Zurich, Binzmühlestrasse 14/19, 8050 Zurich, Switzerland

[5] University of Bern, Clinical Psychology and Psychotherapy, Fabrikstrasse 8, 3012 Bern, Switzerland

[6] Department of Psychiatry and Psychotherapy III, University of Ulm, Leimgrubenweg 12-14, 89075 Ulm, Germany

[7] Behavioural and Clinical Neuroscience Institute and Department of Psychiatry, University of Cambridge, Downing Street, Cambridge, CB2 3EB, United Kingdom

Corresponding author:

PD Dr. Annette Beatrix Brühl, M.D.

Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich

Lenggstrasse 31, CH-8032 Zurich, Switzerland

Current address: Behavioural and Clinical Neuroscience Institute and Department of Psychiatry, University of Cambridge, Downing Street, Cambridge, CB2 3EB, United Kingdom

Accepted for publication in European Archives of Psychiatry and Clinical Neuroscience

Abstract

Dealing with one's emotions is a core skill in everyday life. Effective cognitive control strategies have been shown to be neurobiologically represented in prefrontal structures regulating limbic regions. In addition to cognitive strategies, mindfulness-associated methods are increasingly applied in psychotherapy. We compared the neurobiological mechanisms of these two strategies, i.e., cognitive reappraisal and mindfulness, during both the cued expectation and perception of negative and potentially negative emotional pictures. Fifty-three healthy participants were examined with functional magnetic resonance imaging (47 participants included in analysis). Twenty-four subjects applied mindfulness, 23 used cognitive reappraisal. On the neurofunctional level, both strategies were associated with comparable activity of the medial prefrontal cortex and the amygdala. When expecting negative versus neutral stimuli, the mindfulness group showed stronger activations in ventro- and dorsolateral prefrontal cortex, supramarginal gyrus as well as in the left insula. During the perception of negative versus neutral stimuli, the two groups only differed in an increased activity in the caudate in the cognitive group. Altogether, both strategies recruited overlapping brain regions known to be involved in emotion regulation. This result suggests that common neural circuits are involved in the emotion regulation by mindfulness-based and cognitive reappraisal strategies. Identifying differential activations being associated with the two strategies in this study might be one step towards a better understanding of differential mechanisms of change underlying frequently used psychotherapeutic interventions.

Keywords: emotional anticipation, fMRI, amygdala, DLPFC, emotion regulation

Introduction

Successful emotion regulation has been associated with adaptive levels of general health, mental health as well as psychosocial functioning [1-4]. Emotion regulation can be defined as “processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions” [5]. Such processes can be applied consciously, but various automatic and effortless methods to regulate emotions have also been investigated [4,6].

Most research on the neural mechanisms of emotion regulation has concentrated on cognitive emotion-regulation strategies such as cognitive reappraisal (e.g. [7,8], for a review: [9]). Meta-analyses suggest a regulatory influence of prefrontal cortical areas (PFC) - specifically dorsolateral (DLPFC), ventrolateral (VLPFC) and dorsomedial (DMPFC) parts – on subcortical regions such as the amygdala, parahippocampal gyrus, anterior cingulate and the thalamus (see meta-analyses: [9-12]; see also animal models: [13]).

Another approach to dealing with challenging emotional situations is the concept of mindfulness, which has its roots in ancient eastern traditions and meditation [14]. Within the last 20 years, mindfulness practice has found its way into “western” psychotherapy, for example in programs such as mindfulness-based stress reduction (MBSR [15]) or mindfulness-based cognitive therapy (MBCT [16]). Mindfulness has been defined “as paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally” ([14], p. 4).Neurobiological research on mindfulness has investigated distinct aspects of mindfulness in diverse samples, ranging from participants without any experience in mindfulness over inexperienced learners of mindfulness practices (e.g. MBCT) to long-term meditation practitioners [17]. These studies investigated neural correlates of different forms of meditation [18,19] as well as the influence of trait-mindfulness on performance in stressful or emotionally challenging tasks [20,21].

Studies with meditation experts meditating during functional magnetic resonance imaging (fMRI) identified increased recruitment of DMPFC and lateral PFC ([17,18], reviews: [22,23]). Similarly, trained subjects showed increased recruitment of viscerosensitive networks (e.g. insula) and lateral PFC during negative valence processing and sadness provocation [20,21]. However, these findings in prefrontal regions seem to be strongly mediated by meditation experience: Tang and colleagues showed that early- and middle-stage meditators needed *more* effortful control to achieve a meditative state compared to expert meditators [24]: the early stages were accompanied by *increased* recruitment of ventral and dorsal ACC, lateral PFC and parietal areas, whereas in expert meditators, lateral prefrontal and parietal areas were *less* active. A similar pattern was found in another study in expert meditators [25]. Farb and colleagues demonstrated that MBSR training resulted in *decreased* ventral and dorsal MPFC activity and increased recruitment of viscerosensitive networks (e.g. insula) as well as increased lateral prefrontal areas in a focused-attention task [19].

Only few studies, however, have investigated the neural mechanisms of short mindfulness interventions in meditation-naïve subjects. In one of these studies, focused breathing activated parietal and prefrontal structures (e.g. DMPFC, dACC) as well as the insula [26]. Studies on emotional introspection (comparable to mindful awareness of one’s feelings) [27] and on labelling of emotions [28] were both associated with reduced activity in the left amygdala and increased activation in the VLPFC.

From a theoretical and clinical perspective, studies on short emotion-regulation interventions are valuable as they could contribute to advancing models of emotion regulation and furthermore support the development of personalized treatment strategies in psychotherapy by establishing neurobiological criteria for the selection of emotion regulation strategies for individual patients.

In the present study, we compared the application of short mindfulness-based strategies to reality checking as cognitive reappraisal technique, both during the cued expectation and perception of emotional stimuli. Previous studies have shown that merely expecting emotional stimuli already may function as an emotion eliciting stimulus itself [29,30], possibly even enhancing the subsequent emotional response to perceiving an emotional stimulus [31]. The neural circuits involved in cognitive emotion regulation during the expectation period have been investigated before [8], identifying MPFC and left DLPFC as regulating and diminishing left amygdala activation [8]. Studies on the effect of a cognitive emotion regulation on the perception of emotional pictures found a similar regulatory network [7,32,33].

In the current study, we expected comparable effects of mindfulness-based and cognitive reappraisal strategies during the expectation and the perception of emotional stimuli.

The reviewed literature suggests that at least in early to middle stages of mindfulness training, mindfulness-based strategies recruit similar prefrontal brain regions as cognitive reappraisal strategies. As the direct comparison of these strategies has not been done before, it is difficult to generate specific hypotheses regarding differences in prefrontal activations between these strategies.

Therefore, we hypothesize for the comparison of mindfulness-based and cognitive reappraisal strategies, that

(a) brain regions associated with emotion regulation show similar activations with both strategies (i.e. DMPFC, MPFC) as well as the amygdala as the main structure known to be targeted by these regions [11]. To adhere to the logic of hypothesis testing, we hypothesized that the two groups would differ significantly in these structures.

(b) in contrast to cognitive reappraisal, mindfulness-based strategies are associated with stronger activity in attention-related networks, particularly in parietal and lateral prefrontal regions [26] and in the insula, given the possible body focus in mindfulness instructions (e.g. [26,34]). We tested this hypothesis by conducting a whole-brain analysis.

Material and Methods

Subjects

Fifty-three healthy subjects (31 females; ages 20-55, M = 29.25, SD = 7.51; all right-handed according to the Annett hand preference scale [35]) without any history of neurological or psychiatric illness participated in the study. Exclusion criteria were excessive consumption of alcohol, nicotine or caffeine, intake of medication (except oral contraceptives) or psychotropic drugs, current neurological or psychiatric illness, and fulfilling contra-indications against magnetic resonance imaging (MRI) examinations as assessed by a semi-structured clinically oriented interview (based on the SCID [36], administered by an experienced psychiatrist [ABB]). To obtain a naturalistic variation in the amount of experience with mindfulness practice and to study effects of the mindfulness instruction independent of training, experience with meditation or mindfulness was neither an inclusion nor an exclusion criterion. Meditation experience was only assessed in the mindfulness group; an overview is given in supplementary Table S1 (previously published in [37]). Participants were recruited via mailing lists and personal contacts. All subjects gave written informed consent according to the Declaration of Helsinki [38] and received a financial compensation of 50 Swiss Francs. The study was approved by the local ethics committee of the Canton of Zurich.

Experimental design

Task and stimuli

During functional MRI (fMRI), subjects performed an emotional expectation task (Figure 1, described in [8]). They expected and perceived emotional pictures of known and unknown valence (International Affective Picture System [39]; list of pictures available upon request from the authors) that were presented via digital video goggles (Resonance Technologies, Northridge, CA). Each trial started with a short cue (duration 1000 ms) indicating after an expectation period of 6920 ms the appearance of pictures of positive "ᴗ"(ps), negative "⌒" (ng), neutral "–" (nt) or of unknown valence "|" (uk), which were either positive or negative (50/50). During expectation a blank screen with a small fixation cross was shown followed by the full-screen presentation of a picture of the respective valence (7920 ms). A baseline period with a blank screen shown for 15840 ms allowed the blood oxygen level-dependent signal to level off before the next trial. Participants were instructed to expect the pictures indicated by the cue and to perceive them accordingly.

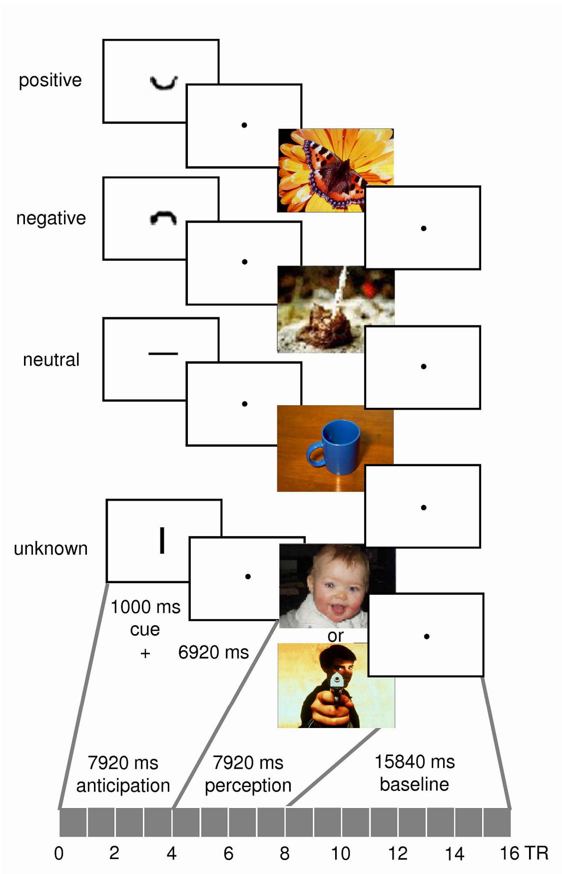

Figure 1 Task and duration, cues are enlarged for presentation reasons (actual height about 1/40 screen size).

The task was programmed with Presentation^{TM} (Neurobehavioral Systems, USA) and consisted of one run (total duration: 30 min) with 56 pseudo-randomized trials comprising 14 trials for each condition of known valence (positive, negative, neutral) and 14 trials for unknown valence. The cues were intuitively understandable and used only few cognitive resources. Pictures were matched for valence-difference from neutral, for complexity of content and, as far as possible, for arousal, based on a prior behavioural study in which subjects rated a set of IAPS pictures (for a discussion of arousal matching, see [8]). Furthermore, the task did not require any motor reaction that could have interfered with the subjects' performance.

After scanning, participants were shown the pictures as printouts again and rated the emotional valence of the presented stimuli on a 9-point-Likert scale (1= most negative; 9 = most positive). Additionally subjects completed a structured interview about their general ability to perform the task, and in the mindfulness group, about the regulation strategies they had employed (focusing on feelings, thoughts or bodily sensations).

Task Instructions

Subjects were assigned to the cognitive reappraisal group or the mindfulness group. For organizational reasons, assignment to the two groups/interventions was not randomized, as the two groups were recruited after each other (separate ethical approvals). The data of the mindfulness group has been previously published [37], but the data of the cognitive control group has not been analysed before. The assignment to the groups was age- and gender-matched. All participants were instructed to apply the respective strategy only during the negative and the "unknown" expectation and perception trials, assuming that in real life these situations are most stressful and more likely require emotion-regulation strategies. In pleasant and neutral conditions, participants in both groups were instructed to expect and observe the pictures. The pleasant conditions were primarily used for assuring a balanced emotional valence of the stimuli and to avoid any negative mood induction.

Participants were given written instructions that were orally recapitulated by the main investigators and participant's questions were answered. Subsequently, participants summarized the instructions in their own words and were given as much time as they needed until the investigators decided that a participant had fully understood the instruction. Afterwards, subjects underwent a training session until they felt comfortable with the task and their instruction during the task. Instruction and training session usually lasted for 10-15 minutes. Pictures shown in the training session were not presented in the main task.

Participants in the mindfulness group were given an instruction on mindful awareness, in which the terms "mindfulness" and "regulation" were not mentioned. Instead, common aspects of mindfulness definitions – non-judgmental awareness of the present moment and openness to experience [14,40] – were used: "Try to consciously be aware of yourself, of what happens to you and within you at this moment. Do this while expecting the picture and while looking at it. Do not judge; remain conscious of and attentive to your present state. You may focus on thoughts, on emotions, or on bodily sensations" [37]. The cognitive reappraisal group was instructed to perform a mental operation that was called "reality checking" during the unpleasant and unknown expectation conditions. This mental operation is comparable to standard interventions used in cognitive behavioural therapy [41-43]. Subjects were instructed to realistically evaluate the context of their current situation during the expectation of the emotional picture, to think e.g. "I am lying in a scanner", "They will show me a picture, this is part of the study" [8].

FMRI acquisition

Imaging was performed using a General Electric 3.0 T SignaTM HD Scanner equipped with an 8-channel head coil (GE Medical Systems, Milwaukee, USA). Across a single functional run, 908 functional volumes (16 per trial) were obtained from 22 sequential axial slices covering whole brain (repetition time/echo time (TR/TE) 1980/32 ms, slice thickness 3.5 mm with 1 mm gap, voxel size 3.125 x 3.125 x 4.5 mm, field of view 200 mm, flip angle 70°). The first four volumes were discarded to allow for T1* equilibration effects. High resolution anatomical volumes were acquired for co-registration with functional data (TR/TE 9.2/2.1; 1x1x1 mm^3 resolution, axial orientation). T2-weighted functional magnetic resonance images were obtained to exclude possible T2-sensitive brain abnormalities.

FMRI data analysis and statistics

FMRI Data were analyzed using BrainVoyagerTM QX 2.4 (Brain Innovation, Maastricht, The Netherlands, [44]). The functional data were pre-processed to maximize signal-to-noise contrast. Pre-processing included motion correction, slice scan time correction, high frequency temporal filtering and linear detrending. Functional images were superimposed on the 2D anatomical images and incorporated into 3D data sets. Each data set was converted to Talairach space [45], resulting in a voxel size of 3x3x3 mm^3, followed by spatial smoothing with an 8 mm Gaussian kernel for subsequent group analysis.

The design matrix consisted of eight predictors representing the expectation (exp) and perception (per) periods of each valence (ng, ps, nt, uk) and the additional factor “group”. These conditions were modelled as epochs using a two-gamma hemodynamic response function. FMRI data analysis comprised the following steps according to the general linear model (GLM). First, we calculated fixed-effects analyses for each subject for the three contrasts comparing the emotion regulation conditions to the respective neutral conditions: The emotion expectation conditions “exp ng > nt” and “exp uk > nt” and the perception condition “per ng > nt”. Second, we calculated a random effects group comparison on the “mindful” and the “cognitive control” group for the brain activation in the selected contrasts on the whole-brain level. Results are reported on a voxel-wise statistical level of $p < .005$. To avoid alpha error-accumulation, Monte-Carlo-Correction [44] was applied, resulting in cluster thresholds of 918 mm^3 (exp ng >

nt), 701 mm^3 (per ng > nt) and 665 mm^3 (exp uk > nt), each resulting in a cluster-wise p < .05. Due to the focus on regulating and regulated structures, we performed ROI-analyses on the three contrasts in bilateral anterior MPFC, DMPFC and bilateral amygdala using cubic ROIs with an edge-length of 15, 12 and 9 mm, respectively (details in Table 1). For further details on the ROI definitions, we referred to Lutz et al. [37]. We controlled for general attention and performance by examining individual brain activity in the primary visual cortex, as brain activity would have decreased as a result of closed eyes or diverted gaze. ROI analyses investigating hemodynamic differences in V1 (cubic ROI, 9 mm edge length, Table 1) revealed no significant differences between both groups. Identification of anatomical regions was based on Talairach atlas [45] and Talairach daemon [46].

Table 1

ROI group analysis in the mindfulness group versus the cognitive control group

ROI Coordinates	Cluster size mm^3	Exp ng > nt		Exp uk > nt		Per ng > nt	
x / y / z		t	p (d)	t	p (d)	t	p (d)
Amygdala R 19 / -8 / -15	729	.14	.89(.04)	.93	.36 (.28)	-.87	.39 (-.26)
Amygdala L -19 / -8 / -15	729	.345	.73 (.10)	.59	.56 (.18)	-0.59	.56 (-.18)
MPFC R 7 / 57 / 23	3375	-.975	.33 (-.29)	-.807	.42 (-.24)	-1.798	.08 (-.54)
MPFC L -7 / 57 / 23	3375	-.686	.50 (-.21)	-.702	.49 (-.21)	-1.517	.14 (-.45)
V1 R 5 / -86 / -3	729	1.08	.29 (.32)	-.25	.80 (-.07)	.67	.50 (.20)

V1 L	729	1.05	.30 (.31)	.20	.84 (.06)	.25	.81 (.07)
- 5 / -86 / -3							
DMPFC R	1728	1.29	.21(.38)	1.30	.20(.39)	-.77	.44(-.23)
6/6/50							
DMFPC L	1728	1.88	.07(.56)	1.18	.24(.35)	-.51	.61(-.15)
-6/6/50							

ROI analysis of emotion *expectation negative versus neutral* (exp ng > nt*), expectation unknown versus neutral* (exp uk > nt), and *perception unknown versus neutral* (per ng > nt) in the mindfulness group compared to the cognitive control group. There were no significant differences ($p < .05$). Effect sizes are indicated in brackets. Abbreviations: V1 primary visual cortex, MPFC medial prefrontal cortex, DMPFC dorsal medial prefrontal cortex, R right, L left

Questionnaires

Prior to scanning all participants completed German versions of self-report questionnaires assessing depression (Self-Rating Depression Scale, SDS [47]), anxiety (State-Trait Anxiety-Inventory, STAI [48]), as well as neuroticism and extraversion (Eysenck Personality Inventory, EPI [49]), and emotion regulation (Emotion Regulation Questionnaire, ERQ [43]). The mindfulness group additionally completed two self-report questionnaires assessing trait mindfulness (Mindfulness Attention and Awareness Scale, MAAS [40]; Freiburg Mindfulness Inventory, FMI [50]). Statistical analyses were performed by SPSS18.0 using student´s t-test and χ^2-tests, statistical significance level $p < .05$.

Results

Participants

Twenty-seven subjects were assigned to the cognitive reappraisal group (4 excluded due to excessive head movements with more than 3 mm in translation and/or rotation), and 26 subjects were assigned to the mindfulness group (1 subject excluded due to reported drowsiness, 1 due to excessive head movements). The final analysis included 23 subjects in the cognitive reappraisal group and 24 in the mindfulness group, totalling 47 subjects (ages 20-55, Mage = 29.06, SD = 7.83, 30 females). The two groups did not differ significantly in terms of age (t (45) = -.42, p = .67), gender distribution ($\chi 2$ (1) = .17, p = .68), and education ($\chi 2$ (3) = 1.15, p = .76), with mostly students in both groups (mind = 14, cog = 15).

Psychometric assessment revealed no clinically relevant degrees of depression or anxiety in any of participants ([51], supplementary Table S2), and the two groups did not differ significantly in their levels of depression, anxiety, neuroticism and extraversion. The mindfulness scores (MAAS, FMI) in the mindfulness group were highly intercorrelated (r = .52, p = .01; N = 24).

Behavioural Data

The mean ratings of emotional valence for positive (M= 7.26, SD = .72; p = .98), negative (3.01, SD =.72, p = .72) and neutral pictures (M=5.20, SD = .22, p = .37) did not differ significantly between the two groups (supplementary Table S2). Internal consistencies for positive (Cronbach's α = .91) and negative valences (α = .90) showed very good reliabilities. Only the neutral valence demonstrated a poor internal consistency (α = .43). The valence ratings of our sample did not differ significantly from IAPS standard values (t_{nt} = .40, p = .69; t_{neg} = 35, p = .73; t_{pos} = .50, p = .62).

After scanning, subjects in both groups confirmed their ability to follow the instructions of cognitive reappraisal or of mindfulness, respectively. Subjects' primary focus of attention in the mindfulness group was almost evenly distributed on feelings (n = 10), thoughts (n = 7) and bodily sensations (n = 7).

FMRI results

The hypothesis-driven ROI analysis in bilateral amygdala, MPFC and DMPFC revealed no differences between the two groups in the investigated contrasts (Table 1). However, the whole-brain group comparison for the expectation of negative > neutral stimuli (Table 2A) revealed significantly higher activations in the mindfulness group compared to the reappraisal group in bilateral inferior frontal gyrus (IFG, Figure 2A-C) as part of the VLPFC, extending into the anterior insula on the left side, as well as bilateral supramarginal gyrus (SMG), and the left DLPFC. During the expectation of unknown announced > neutral pictures, the mindfulness group had significantly higher activations in the left DLPFC (Table 2B). The perception of negative > neutral pictures was associated with significantly decreased activations in the mindfulness compared to the reappraisal group in the caudate head (Figure 3).

Table 2

Whole-brain group comparison mindfulness > cognitive control

Anatomic region	Brodmann area	Cluster size (mm^3)	Talairach coordinates			t-max	p-max
			X	Y	Z		
A. Expectation of negative emotional stimuli (negative > neutral)							
MidFG/DLPFC L	8	3942	-37	34	45	4.30	0.00009
IFG/PreCentG R, divided into	45/44	4557	56	16	3	6.00	0.00000
a) IFG/VLPFC R	43/4	1989	50	-5	12	3.99	0.00024
b) IFG/VLPFC R	45/44	2397	56	16	3	6.00	0.00000
IFG L, divided into	47	11177	-34	31	-15	4.86	0.00002
a) IFG/ VLPFC L	46/10	3077	-37	40	3	4.47	0.00005
b) Insula/IFG L	13	5126	-34	25	12	4.09	0.00018

IFG L	6/4	2162	-61	-2	21	4.73	0.00002
PreCentG R	4	1013	14	-26	60	3.80	0.00043
SMG R	13/40	1100	47	-26	24	3.93	0.00029
SMG L	40/42	1984	-64	-23	21	3.84	0.00038
B. Expectation of possibly negative emotional stimuli (unknown > neutral)							
SFG/MidFG L	8	1324	-37	25	51	4.56	0.00004
C. Perception of negative emotional stimuli (negative > neutral)							
Caudate Head R		1123	17	22	9	-3.79	0.00045

Activated areas in a random effects analysis (rfx) with a voxel-wise threshold of p < .005 of the contrast mindfulness > cognitive control group. Minimum cluster size (for cluster-wise threshold of p < .05) in contrast A): 896 mm3 (34 functional voxel). Contrast B): 665 mm3 (26 functional voxel). Contrast C): 707 mm3 (27 functional voxel). Larger clusters with several local maxima were manually split into anatomically separate sub-clusters. Given are the Talairach coordinates of the peak voxel.

Abbreviations: IFG Inferior Frontal Gyrus, PreCentG Precentral Gyrus, VLPFC Ventrolateral Prefrontal Cortex, SMG Supramarginal Gyrus, MidFG Middle Frontal Gyrus, DLPFC Dorsolateral Prefrontal Cortex, SFG Superior Frontal Gyrus, R Right, L Left.

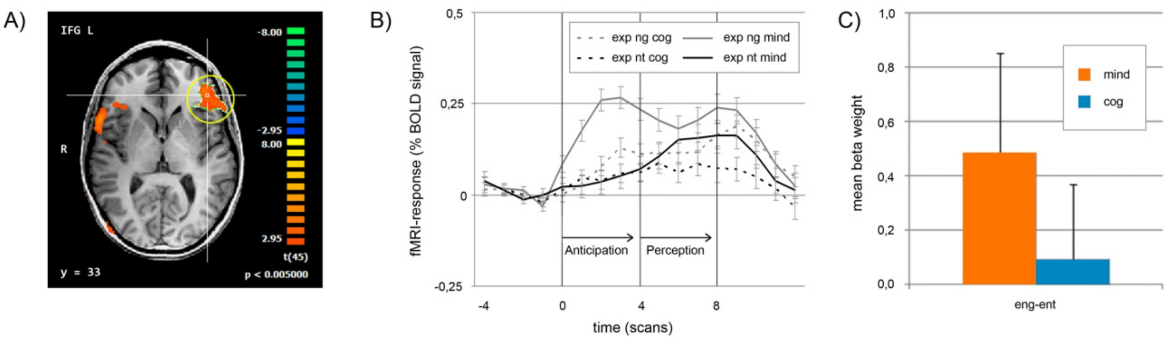

Figure 2 Group comparison mindful > cognitive control during the expectation of negative versus neutral pictures (exp ng>nt). (A) Increased brain activity in the left inferior frontal gyrus in the mindful group (p<.005 voxel-wise, p<.05 cluster wise). (B) Average time courses of activation in this region. Error bars indicate standard error (consider the delay of the hemodynamic response function. (C) Mean beta weights within the IFG (x= -39, y = 33, z = 3) in the mindfulness group (mind) compared to the cognitive reappraisal group (cog). Abbreviations: mind – mindfulness group, cog – cognitive reappraisal group, exp ng – expectation of negative pictures, exp nt – expectation of neutral pictures.

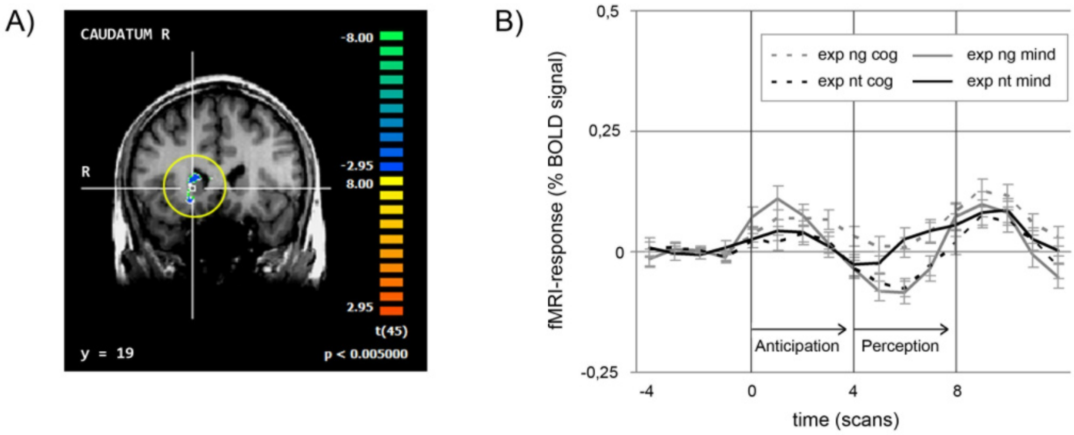

Figure 3 Group comparison during the perception of negative versus neutral pictures (per ng>nt). (A) Lower brain activity in the right caudate in the mindfulness group compared to the cognitive reappraisal group. (B) Average time courses of activation in this region. Error bars indicate standard error (consider the delay of the hemodynamic response function). Abbreviations: mind – mindfulness group, cog – cognitive reappraisal group, per ng – perception of negative pictures, per nt – perception of neutral pictures

Discussion

We compared the neural correlates of a mindfulness-based and a cognitive reappraisal strategy during the expectation and perception of emotionally arousing stimuli. The application of mindfulness-based and cognitive reappraisal strategies in an emotional context showed comparable effects on the level of activation in the amygdala as the central emotion-processing structure. Whereas the neural circuits partly overlapped between these two strategies, they also showed differences, suggesting the employment of partly distinct psychological mechanisms with distinct neural representations for emotion regulation.

Shared circuits between mindfulness-based and cognitive reappraisal strategy

Both groups did not differ in their activations in the DMPFC, anterior MPFC and the amygdala in nearly all investigated contrasts. This suggests that the regulating structures as well as the target regions (amygdala) are shared by the two strategies.

Differences, however, might be based on differential time courses of the two strategies. It could be argued that mindfulness, once activated, has a slightly more sustained effect, thus subsequently requiring less mental effort for maintaining regulation in contrast to a more rapidly fading effect of the cognitive reappraisal strategy. However in the present study as in the literature, there are overall comparable activations of the DMPFC, MPFC and amygdala in mindfulness-based and cognitive reappraisal strategies [10,11,13]. This could reflect a common regulatory network generally activated by several emotion regulation strategies [11].

Differential mechanisms of mindfulness-based and cognitive reappraisal strategies

In summary, the use of mindfulness-based strategies for emotion regulation as compared to cognitive reappraisal during the expectation of negative stimuli was associated with *stronger* activations in left DLPFC, bilateral VLPFC and bilateral SMG. Differences between the two strategies were similar, but less pronounced during the expectation of previously announced unknown, possibly negative pictures. During the perception of negative stimuli, the application of mindfulness was associated with *reduced* activation in right caudate head compared to cognitive reappraisal.

The VLPFC/IFG region has previously been activated bilaterally with cognitive reappraisal (compared to no explicit control [8]) and with regulatory functions in other domains such as response inhibition [52,53] and affect labelling [28]. A prior study on affect labelling (which could be considered as a reduced mindfulness intervention) found similar activation in the right VLPFC [28]. Furthermore, several studies implicated the IFG in self-awareness and self-referential processing, particularly when emotions were involved [54-56].

In the current study, the stronger activation of the VLPFC during emotional expectation in the mindfulness group could either reflect the involvement of different neural circuits for mindful emotion regulation in comparison to cognitive reappraisal or it could be related to a stronger involvement of brain structures associated with self-referential information processing [57,58].

Stronger activation of the insula has been found (in parallel to activation in the VLPFC) in studies investigating expressive suppression [9], mindful affect labelling of negative affective stimuli [34], and also cognitive reappraisal during the expectation of negative events [59], pointing to the insula playing a role in regulatory processes. Additionally, the insula has been found to be associated with awareness of one's own body [60] as in focused breathing [26] and with viscerosensitive processing [61], potentially reflecting a focus on bodily sensations in mindfulness meditation [57]. In our study, increased insula activity might represent either the allocation of more regulatory resources in the mindfulness-based strategy or a response to the focus on bodily sensations in the mindfulness-based instruction. However, we cannot separate these two processes in the current study.

In the mindfulness group, stronger activation in the bilateral SMG during the expectation of negative emotional stimuli could be related to emotion regulation, comparable as to what has been shown for reappraisal [7,62], for focused attention and meditation states [63] .These findings suggest that increased neural resources are required for the initial phase of mindful regulation.

In the current study, the mindfulness-based strategy was associated with increased activity in the left DLPFC during expecting negative emotional stimuli compared to the cognitive reappraisal strategy. Left DLPFC was more active also when comparing cognitive reappraisal to no control in prior studies [7,8]. As cognitive reappraisal and mindfulness-based strategies have not been compared directly before, it may be tentatively concluded that DLPFC resources are likely to be important in both strategies. However, the early phase of mindfulness seems to require more DLPFC resources.

Interestingly, the differences between mindfulness-based and cognitive reappraisal-based emotion regulation were less pronounced during the expectation of stimuli being announced as "unknown". In this study, we found an increased activity in the left

DLPFC (and at an exploratory level in left VLPFC and right SMG) only when mindfulness was applied. This finding stands in contrast to a large body of literature on uncertainty (for example [64-66]), and may suggest higher levels of arousal in uncertain situations, consequently requiring more regulatory efforts. Further research is needed to clarify this apparent contradiction.

During the perception of negative versus neutral stimuli, mindfulness-based and cognitive reappraisal strategies differed solely in the activation of one region, i.e., the caudate head. Compared to mindfulness, activity in the caudate was *increased* in the cognitive reappraisal group. The caudate as part of the striatum has been associated with motor control [67], with learning and memory functions [68], with response inhibition [69] as well as with cognitive and emotional processing [70,71]. Furthermore, the caudate has been found to be modulated by regulatory strategies [9]. Graybiel summarized the general role of the caudate as playing a major role in optimal motor function and cognitive reappraisal [72], particularly in automated or habitual motor and cognitive processes [70,73].

With regard to the comparison between mindfulness and cognitive reappraisal, the activation in the caudate in the cognitive reappraisal group is not obviously clear. On the one hand, subcortical structures including the caudate were more active during focused breathing [26], and a meta-analysis revealed stronger activations in the left caudate body and the MPFC during meditation when compared with rest or control conditions [74]. Considering the previously shown relevance of the caudate particularly in well-learned cognitive circuits, our results might eventually be explained with the assumption that cognitive reappraisal might constitute a better establishes routine as opposed to mindfulness. This especially in a sample of participants from a “western” cultural background with mostly no or very little mindfulness experience. On the other hand, the caudate was not activated stronger in beginners during a short mindfulness task when compared to experienced meditators [75]. Therefore, our results await replication in future studies and further research is needed for clarifying the caudate’s role in processes involving mindfulness and emotion-regulation strategies.

Limitations

One possible limitation of this study is that no behavioural control was used. We intentionally chose this approach to prevent potential interference due to preparatory and executive processes during task performance as suspected in previous studies using this paradigm (e.g. [8]). Nevertheless, it is difficult to draw conclusions concerning the subjectively experienced efficiency of the applied strategies.

Another limitation is that subjects were not homogeneous in their experience with mindfulness. This approach was chosen to study the neural correlates of the initialization of mindfulness at a more general level. However, this heterogeneity within the sample might have influenced some neural responses.

Additionally, the stimuli were only rated on subjective valence, but not on evoked arousal after the scan, so that an experience of arousal in the scanner can only be assumed. The choice of a between-groups-design with no randomization and the probability of unaccounted group differences have to be regarded as a limitation. In the current study, we wanted to prevent possible mixing of strategies by participants and therefore decided to instruct the participants in separate groups. Future studies could implement within-group-comparisons to address this concern.

Future perspectives

In future applications, our results might contribute to the development of individualized therapy plans for people presenting with mental disorders. The neurobiological markers linked to distinct emotion regulation strategies could assist therapists in choosing emotion-regulation strategies that optimally match the patient’s strengths and deficits. For example, the results of an fMRI scan may help to choose between mindfulness-focused strategies vs. cognitive reappraisal strategies for emotion regulation.

In addition, future research may vary the length of the expectation period or may subdivide this period, to see if distinct activations can be identified with different time courses. Furthermore, it would be of interest to compare trained with untrained meditators, as trained meditators may need lesser resources to initiate a mindful state and may be more effective in applying mindfulness-based strategies without facing concrete negative stimuli at all.

Concluding remarks

To summarize, the results of this study demonstrate that mindfulness strategies during emotional stimulation seem to recruit similar brain circuits as cognitive strategies. Also, mindful emotion regulation appears to exert a similar effect as cognitive emotion regulation onto the amygdala, figuring as a main brain region for emotional processing. These commonalities between mindfulness and cognitive reappraisal support prior findings of an emotion regulating effect of mindfulness without requiring an explicit regulatory intention or needing intensive training. The more pronounced activation of VLPFC, left DLPFC, SMG, and insula with mindfulness as compared to cognitive reappraisal during the expectation, but not the perception of negative stimuli lead to the following tentative conclusion: Whereas at the outset, the early initiation of a mindful state may claim more cognitive resources than cognitive reappraisal in this expectant situation, once activated, mindful processing may not require more prefrontal activation than cognitive reappraisal does. This reasoning is consistent with the proposition that, particularly in untrained participants, mindfulness could be considered a top-down emotion-regulation process involving an increased activation of PFC areas [76].

Implications of our study for clinical practice may be seen in the use of the individual's neurobiological activation pattern associated with different emotion regulation strategies for a differential diagnosis of strengths and deficits of the patients and for adapted therapy indications.

Funding: This work was supported by Swiss National Science Funds (SNSF) grant No. 3200B0 12120. The SNSF had no influence on study design, data analysis and interpretation and manuscript preparation.

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Supplementary Material

Table S1

Meditation and similar experiences in the Mindfulness Group

	Present (N)	Past (N)	Total anytime (N)
Meditation experience [a]	4	5	9
Related experience [b]	4	8	12

Note. Altogether, 9 subjects had no experience in either meditation or related techniques, 17 subjects don't practice either meditation or related techniques momentarily. 4 subjects were currently practicing meditation techniques ranging from irregular and short sessions to 10 hours a week in one subject.

[a] Meditation experience in this group: Mindfulness/Vipassana Meditation, Movement meditation, Focused breathing.

[b] Related experiences in this group: Autogenous training, Yoga, Tai Chi, Relaxation Training.

Table S2

Psychometric measures of included subjects per group

Scale	Mind M (SD, N)	Cog M (SD, N)	t-test Mind-Cog	
			T	p (d)
SDS	36.03 (6.34, 23)	36.14 (6.75, 22)	-.053	.96 (-.02)
STAI-S	30.79 (5.65, 24)	31.67 (5.84, 21)	-.510	.61 (-.16)
STAI-T	30.88 (8.22, 24)	35.95 (8.87, 22)	-.075	.94 (-.02)
EPI-N	6.29 (3.03, 24)	8.91 (4.1, 22)	-.571	.57 (-.17)
EPI-E	13.71 (4.50, 24)	11.73 (3.97, 22)	.455	.65 (.14)
ERQ Reapp.	4.89 (.85, 25)	4.90 (1.09, 22)	-.044	.97 (-.01)
ERQ Suppr.	3.15 (1.05, 24)	2.65 (.09, 22)	1.726	.09 (.52)
MAAS	67.04 (9.43, 24)			
FMI	37.67 (5.93, 24)			
Rating positive pictures (valence)			.027	.979
Rating negative pictures (valence)			-.358	.722
Rating neutral pictures (valence)			.907	.369

References

1. John OP, Gross JJ (2004) Healthy and unhealthy emotion regulation: personality processes, individual differences, and life span development. J Pers 72 (6):1301-1333.

2. Gross JJ (2002) Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 39 (3):281-291.

3. Eftekhari A, Zoellner LA, Vigil SA (2009) Patterns of emotion regulation and psychopathology. Anxiety Stress Coping 22 (5):571-586.

4. Koole SL (2009) The psychology of emotion regulation: An integrative review. Cogn Emot 23 (1):4 - 41.

5. Gross JJ (1998) The Emerging Field of Emotion Regulation: An Integrative Review. Rev Gen Psychol 2 (3):271-299.

6. Mauss IB, Bunge SA, Gross JJ (2007) Automatic emotion regulation. Soc Personal Psychol Compass 1 (146-167).

7. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JDE (2002) Rethinking Feelings: An fMRI Study of the Cognitive Regulation of Emotion. J Cogn Neurosci 14 (8):1215-1229.

8. Herwig U, Baumgartner T, Kaffenberger T, Brühl A, Kottlow M, Schreiter-Gasser U, Abler B, Jäncke L, Rufer M (2007) Modulation of anticipatory emotion and perception processing by cognitive control. NeuroImage 37 (2):652-662.

9. Ochsner KN, Silvers JA, Buhle JT (2012) Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci 1251 (1):E1-E24.

10. Kalisch R (2009) The functional neuroanatomy of reappraisal: time matters. Neurosci Biobehav Rev 33 (8):1215-1226.

11. Diekhof EK, Geier K, Falkai P, Gruber O (2011) Fear is only as deep as the mind allows: A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. NeuroImage 58:275-285.

12. Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, Weber J, Ochsner KN (in press) Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. Cereb Cortex. doi:10.1093/cercor/bht154.

13. Quirk GJ, Beer JS (2006) Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr Opin Neurobiol 16 (6):723-727.

14. Kabat-Zinn J (1994) Wherever you go, there you are: Mindfulness meditation in everyday life. Hyperion, New York.

15. Kabat-Zinn J (1990) Full Catastrophe Living. Bantam Doubleday Publishing Group, Inc., New York.

16. Segal ZV, Williams JM, Teasdale JD (2001) Mindfulness-Based Cognitive Therapy for Depression: A New Approach to Preventing Relapse. Guilford Press, New York.

17. Hölzel BK, Ott U, Hempel H, Hackl A, Wolf K, Stark R, Vaitl D (2007) Differential engagement of anterior cingulate and adjacent medial frontal cortex in adept meditators and non-meditators. Neurosci Lett 421 (1):16-21.

18. Hasenkamp W, Wilson-Mendenhall CD, Duncan E, Barsalou LW (2012) Mind wandering and attention during focused meditation: a fine-grained temporal analysis of fluctuating cognitive states. Neuroimage 59 (1):750-760.

19. Farb NA, Segal ZV, Mayberg H, Bean J, McKeon D, Fatima Z, Anderson AK (2007) Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. Soc Cogn Affect Neurosci 2 (4):313-322.
doi:10.1093/scan/nsm030

20. Farb NA, Anderson AK, Mayberg H, Bean J, McKeon D, Segal ZV (2010) Minding One's Emotions: Mindfulness Training Alters the Neural Expression of Sadness. Emotion 10 (1):25-33.

21. Allen M, Dietz M, Blair KS, van Beek M, Rees G, Vestergaard-Poulsen P, Lutz A, Roepstorff A (2012) Cognitive-affective neural plasticity following active-controlled mindfulness intervention. J Neurosci 32 (44):15601-15610.

22. Cahn BR, Polich J (2006) Meditation states and traits: EEG, ERP, and neuroimaging studies. Psychol Bull 132 (2):180-211.

23. Chiesa A, Serretti A (2010) A systematic review of neurobiological and clinical features of mindfulness meditations. Psychol Med 40 (8):1239-1252.

24. Tang YY, Rothbart MK, Posner MI (2012) Neural correlates of establishing, maintaining, and switching brain states. Trends Cogn Sci 16 (6):330-337.

25. Ives-Deliperi VL, Solms M, Meintjes EM (2011) The neural substrates of mindfulness: an fMRI investigation. Soc Neurosci 6 (3):231-242.

26. Dickenson J, Berkman ET, Arch J, Lieberman MD (2013) Neural correlates of focused attention during a brief mindfulness induction. Soc Cogn Affect Neurosci 8 (1):40-47. doi:10.1093/scan/nss030.

27. Herwig U, Kaffenberger T, Jäncke L, Brühl AB (2010) Self-related awareness and emotion regulation. NeuroImage 50 (2):734-741.

28. Lieberman MD, Eisenberger NI, Crockett MJ, Tom SM, Pfeifer JH, Way BM (2007) Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. Psychol Sci 18 (5):421-428.

29. Herwig U, Kaffenberger T, Baumgartner T, Jäncke L (2007) Neural correlates of a 'pessimistic' attitude when anticipating events of unknown emotional valence. Neuroimage 34 (2):848-858.

30. Bermpohl F, Pascual-Leone A, Amedi A, Merabet LB, Fregni F, Gaab N, Alsop D, Schlaug G, Northoff G (2006) Dissociable networks for the expectancy and perception of emotional stimuli in the human brain. Neuroimage 30 (2):588-600.

31. Vrana SR, Spence EL, Lang PJ (1988) The startle probe response: A new measure of emotion? J Abnorm Psychol 97 (4):487-491.

32. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ (2004) For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage 23 (2):483-499.

33. Goldin PR, McRae K, Ramel W, Gross JJ (2008) The neural bases of emotion regulation: reappraisal and suppression of negative emotion. Biol Psychiatry 63 (6):577-586.

34. Creswell JD, Way BM, Eisenberger NI, Lieberman MD (2007) Neural correlates of dispositional mindfulness during affect labeling. Psychosom Med 69 (6):560-565.

35. Annett M (1970) A classification of hand preference by association analysis. Br J Psychol 61 (3):303-321.

36. First MB, Spitzer RL, Gibbon M, Williams JBW (2002) Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). Biometrics Research, New York.

37. Lutz J, Herwig U, Opialla S, Hittmeyer A, Jancke L, Rufer M, Grosse Holtforth M, Bruhl AB (in press) Mindfulness and Emotion Regulation - an fMRI Study. Soc Cogn Affect Neurosci.

38. World Medical Association (2008) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. World Medical Association, Ferney-Voltaire, France.

39. Lang PJ, Bradley, M.M., Cuthbert, B.N. (2005) International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6. Center for Research in Psychophysiology, University of Florida, Gainesville, FL.

40. Brown KW, Ryan RM (2003) The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol 84 (4):822-848.

41. Beck AT, Rush AJ, Shaw BF, Emery G (1979) Cognitive Therapy of Depression. The Guilford Clinical Psychology and Psychotherapy Series. Guilford Press, New York.

42. Hand I (2000) Group exposure in vivo for agoraphobics (1974): a multifaceted pilot study and its impact on subsequent agoraphobia research. Behav Cogn Psychother 28 (04):335-351.

43. Gross JJ, John OP (2003) Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol 85 (2):348-362.

44. Goebel R, Esposito F, Formisano E (2006) Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: From single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. Hum Brain Mapp 27 (5):392-401.

45. Talairach J, Tournoux P (1988) Co-planar Stereotaxic Atlas of the Human Brain: Three-dimensional Proportional System. Thieme Medical, New York.

46. Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10 (3):120-131.

47. Zung WW (2005) Self-Rating Depression Scale. In: Cips CIPS (ed) Internationale Skalen für Psychiatrie. Beltz, Göttingen.

48. Laux L, Glanzmann P, Schaffner P, Spielberger CD (1981) Das State-Trait-Angstinventar. Beltz, Weinheim.

49. Eysenck HJ, Eysenck SB (1964) Manual of the Eysenck Personality Inventory. 4 edn. University of London Press, London.

50. Walach H, Buchheld N, Buttenmüller V, Kleinknecht N, Schmidt S (2006) Measuring mindfulness--the Freiburg Mindfulness Inventory (FMI). Personal Indiv Differ 40 (8):1543-1555.

51. Crawford J, Cayley C, Lovibond PF, Wilson PH, Hartley CA (2011) Percentile Norms and Accompanying Interval Estimates from an Australian General Adult Population Sample for Self-Report Mood Scales (BAI, BDI, CRSD, CES-D, DASS, DASS-21, STAI-X, STAI-Y, SRDS, and SRAS). Australian Psychologist 46:3-14.

52. Collins HR, Corbly CR, Liu X, Kelly TH, Lynam D, Joseph JE (2012) Too little, too late or too much, too early? Differential hemodynamics of response inhibition in high and low sensation seekers. Brain Res 1481:1-12.

53. Zhang J, Hughes LE, Rowe JB (2012) Selection and inhibition mechanisms for human voluntary action decisions. Neuroimage 63 (1):392-402.

54. Morin A, Michaud J (2007) Self-awareness and the left inferior frontal gyrus: inner speech use during self-related processing. Brain Res Bull 74 (6):387-396.

55. Liakakis G, Nickel J, Seitz RJ (2011) Diversity of the inferior frontal gyrus--a meta-analysis of neuroimaging studies. Behav Brain Res 225 (1):341-347.

56. Morin A, Hamper B (2012) Self-reflection and the inner voice: activation of the left inferior frontal gyrus during perceptual and conceptual self-referential thinking. Open Neuroimag J 6:78-89.

57. Hayes SC, Villatte M, Levin M, Hildebrandt M (2011) Open, aware, and active: contextual approaches as an emerging trend in the behavioral and cognitive therapies. Annu Rev Clin Psychol 7:141-168.

58. Farb NA, Anderson AK, Segal ZV (2012) The mindful brain and emotion regulation in mood disorders. Can J Psychiatry 57 (2):70-77.

59. Ochsner KN, Gross JJ (2005) The cognitive control of emotion. Trends Cogn Sci 9 (5):242-249.

60. Craig AD (2010) Once an island, now the focus of attention. Brain Struct Funct 214 (5-6):395-396.

61. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ (2004) Neural systems supporting interoceptive awareness. Nat Neurosci 7 (2):189-195.

62. Goldin PR, Manber T, Hakimi S, Canli T, Gross JJ (2009) Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. Arch Gen Psychiatry 66 (2):170-180.

63. Tomasino B, Fregona S, Skrap M, Fabbro F (2013) Meditation related activations are modulated by the practices needed to obtain it and by the expertise: an ALE meta-analysis study. Frontiers in Human Neuroscience 6. doi:10.3389/fnhum.2012.00346

64. Nesse RM (2000) Is Depression an Adaptation? Arch Gen Psychiatry 57 (1):14-20. doi:10.1001/archpsyc.57.1.14

65. Panksepp J (2006) Emotional endophenotypes in evolutionary psychiatry. Prog Neuro-Psychopharmacol Biol Psychiatry 30 (5):774-784.

66. Simmons A, Matthews SC, Paulus MP, Stein MB (2008) Intolerance of uncertainty correlates with insula activation during affective ambiguity. Neurosci Lett 430 (2):92-97.

67. Rosenbaum DA (2010) Human motor control. 2nd edn. Academic Press/Elsevier, San Diego.

68. Packard MG, Knowlton BJ (2002) Learning and memory functions of the Basal Ganglia. Annu Rev Neurosci 25:563-593.

69. Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26 (9):2424-2433.

70. Middleton FA, Strick PL (2000) Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Brain Res Rev 31 (2-3):236-250.

71. Monk CS (2008) The development of emotion-related neural circuitry in health and psychopathology. Dev Psychopathol 20 (4):1231-1250.

72. Graybiel AM (2005) The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol 15 (6):638-644.

73. Seger CA (2006) The basal ganglia in human learning. Neuroscientist 12 (4):285-290.

74. Sperduti M, Martinelli P, Piolino P (2012) A neurocognitive model of meditation based on activation likelihood estimation (ALE) meta-analysis. Conscious Cogn 21 (1):269-276.

75. Taylor SF, Grant J, Daneault V, Scavone G, Breton E, Roffe-Vidal S, Courtemanche J, Lavarenne AS, Beauregard M (2011) Impact of mindfulness on the neural responses to emotional pictures in experienced and beginner meditators. NeuroImage 57 (4):1524-1533.

76. Chiesa A, Serretti A, Jakobsen JC (2013) Mindfulness: top-down or bottom-up emotion regulation strategy? Clin Psychol Rev 33 (1):82-96.

4. General Discussion

4.1. Main findings

In the last years, interest in the concept of mindfulness has grown quickly, as it has been associated with improved psychological and physiological well-being (Brown & Ryan, 2003; Chiesa & Serretti, 2010). Still the underlying neurobiological correlates and the understanding of its functioning are vague. The presented doctoral thesis intended to add evidence to the research on mindfulness. In the first study, we investigated the neural correlates of a very basic mindfulness intervention, namely emotion introspection, in comparison to cognitive self-reflection. We recruited a sample of depressed patients in the acute and remitted state of depression to gain insight in their ability to engage in mindfulness while in these two states. We expected to find differences reflecting the course of remission. In the second study, we confronted healthy participants with emotionally arousing stimuli and compared mindful emotion regulation to cognitive emotion regulation during the stimulation. We were interested in differences and similarities in the underlying neurobiological correlates of these two interventions. In the following, the results of the two studies will be briefly summarized and a general discussion associating the results of the studies along with their limitations and future research perspectives is given.

The **first study** used a within-subject comparison of acute and remitted depressive patients during self-reflection and emotion introspection and revealed distinct neural activation patterns. Emotion introspection in acute and remitted patients was associated with reduced amygdala and VMPFC activation compared to self-reflection. The reduced amygdala activation lead us to conclude that the ability to use a mindfulness-close approach to regulate ones amygdala activation is intact in acute and remitted depressive patients (Creswell et al., 2007; Herwig et al., 2010; Lieberman et al., 2007). Additionally, VMPFC down-regulation has been associated with mindful states. Our results point therefore to an ability to engage in mindfulness in both states, but also to a further improvement with the course of remission due to stronger VMPFC down-regulation (Farb et al., 2007; Taylor et al., 2011). Moreover, we found a reversed activation of the bilateral middle and inferior temporal gyrus, showing *increased* activation in emotion introspection and *decreased* activation in self-reflection in the acutely depressed state. Contrary, the remitted state was associated with the opposite pattern in this region and stronger activation differences on trend level, namely *decreased* activation during emotion introspection and *increased* during self-reflection. Self-reflection compared to emotion introspection was further associated with increased DLPFC activation in the remitted state. In line with research on semantic processing (Farb et al., 2007; Goel & Dolan, 2001; Whitney et al., 2011), the activation pattern in the middle and inferior temporal gyrus points to a more automated rumination process during self-reflection in acute depression and a more controlled reflection process in the remitted state. This explanation fits with the increased DLPFC activation during self-reflection after remission, also suggesting increased cognitive, reflecting engagement (Herwig et al., 2010; Koenigs & Grafman, 2009; Soares & Mann, 1997). In line with the findings made, the acutely depressed patients showed increased activation in the cuneus during self-reflection compared to emotion introspection, which could correspond to ruminative processes (Cooney et al., 2010). Furthermore, the reduced recruitment of areas associated with semantic processing during emotion introspection in the course of remission could indicate changes in their task performance. Acutely depressed patients might have reflected verbally on their actual feelings, whereas remitted patients might have used less verbal self-instructions and -descriptions. In summary, the results point towards a normalization in brain activation especially for self-reflection with remission and an ability to perform short mindfulness-close interventions in remitted as well as acutely depressed patients.

The **second study** compared mindful and cognitive emotion regulation during the anticipation and perception of emotional stimuli in healthy subjects. Similar activations in the DMPFC, anterior MPFC and in the amygdala suggest a common regulatory network activated by several emotion regulation strategies. This is in line with previous research on such strategies (Buhle et al., 2013; Kalisch, 2009) and fits very well with a recently published study aiming for the comparison of affect labelling and reappraisal (Burklund et al., 2014). An earlier study of our research group had investigated mindfulness without external emotional stimulation (Herwig et al., 2010). To investigate the efficacy and mechanisms of mindfulness during emotional stimulation, we choose a paradigm that had previously been successfully implemented (Herwig et al., 2007). It had been used to investigate neural correlates of anticipation and perception of emotional stimuli in healthy subjects without an explicit instruction (Herwig et al., 2007) and using a cognitive emotion regulation strategy (Herwig et al., 2007).

The anticipation of negative compared to neutral stimuli revealed stronger activations in ventro- and dorsolateral prefrontal areas, supramarginal gyrus and the left insula in the mindfulness group. Thus, the early initiation of mindfulness recruits more prefrontal cognitive resources and bilateral SMG, found to be associated with affect labelling (Herwig et al., 2010), self-awareness and self-referential-processing (Zhang, Hughes, & Rowe, 2012) as well as cognitive reappraisal (Herwig et al., 2007; Ochsner et al., 2002; Ochsner & Gross, 2008).

The increased insula activation might be associated with the focus on bodily sensations (Dickenson et al., 2013) but also with similar regulatory processes as found for the VLPFC (Morin & Hamper, 2012). During the perception of negative compared to neutral stimuli, the two strategies differed only with regards to a reduced activation in the caudate head in the mindfulness group. This result calls for further investigation in future research, as the caudate has on the one hand been associated with motor control and cognitive reappraisal (Middleton, 2000; Nesse, 2000) and on the other hand with focused breathing and meditation practice (Dickenson et al., 2013; Monk, 2008). Thus, we conclude that the early initiation of a mindful state during the anticipation of an emotional stimulus recruits more neural resources compared to cognitive reappraisal. Once activated, mindfulness does not seem to recruit more neural resources in comparison to cognitive reappraisal and can be assumed to have a similar emotion regulating effect.

4.2. Common Ground

On the one hand, we found that mindfulness can be used as an emotion regulation strategy with similar effects compared to cognitive control in healthy subjects, only differing in the need for more cognitive resources during the anticipation of negative stimuli. On the other hand, we found that acutely and remitted depressed patients were able to perform a mindfulness close task, resulting in a down regulation of the amygdala and the VMPFC, as found in previous studies on mindfulness (Farb et al., 2007; Taylor et al., 2011). This means, that healthy subjects as well as acutely and remitted depressive patients are able to perform mindfulness-close interventions resulting in a down-regulation of the amygdala in both tasks, emotion-introspection and mindful anticipation and perception. This is in line with previous research that points to the ability of healthy subjects to engage in emotion introspection and to down-regulate their amygdala (Herwig et al., 2010). Furthermore, studies have shown that even untrained healthy subjects can influence their amygdala activation when performing mindfulness-close interventions such as affect-labelling (Burklund et al., 2014). Our results broaden those findings, showing the comparable effectiveness of mindful and cognitive emotion regulation as well as the ability of acutely and remitted depressed patients to engage in a mindfulness-close intervention. In the theoretical context of the process model of emotion regulation (Gross & Thompson, 2007), our study adds mindfulness as an effective way of dealing with arising emotions.

Brühl (2012) proposes mindfulness to be a strategy influencing the development of an emotion during the whole process from its initial perception to the final reaction. In line with this extension mindfulness can be applied per se without e.g. in the anticipation of an emotional situation and in confrontation with it. The studies presented in this doctoral thesis are embedded in a large ongoing research project on emotion regulation. Previous findings on the anticipation and perception of potentially emotional arousing stimuli without using an emotion regulating strategy pointed to a pessimistic bias in depression (Herwig et al., 2010). This is well in line with Beck's theory of the negative bias towards the self, the world and the future (Beck et al., 1979). Another study with depressed patients performing cognitive emotion regulation revealed comparable effectiveness in the strategy use on the neural level as found for healthy subjects (unpublished data). The study of emotion introspection in healthy subjects revealed a similar decrease in amygdala activation as found in the presented study for acutely and remitted depressed patients (Herwig et al., 2010). First results of an ongoing study of our research group point to neurobiological changes in the course of remission, as we investigate the influence of an MBCT on emotion-introspection and self-reflection in remitted depression. In summary, we have indications that the vulnerability factor depression is reduced within the course of depression, pointing to a normalization of the brain activation. Furthermore, also depressed and remitted depressed patients seem to be able to regulate their emotions effectively. Nevertheless, follow-up investigations are needed to prove whether normalizations persist or whether some differences reappear, potentially in the context of increased depressive symptoms up to depressive relapse.

4.3. Limitations

The two studies, as part of a large research project, use different designs and subject groups, limiting the possibility to draw direct conclusions. Nevertheless, in the context of other studies, the gained insight can be regarded as steps on the way towards an increased understanding of mindfulness and its neural underpinnings. Specifically, the emotion-introspection-task used a mindfulness-close instruction that did not include all core features of the definition of mindfulness, especially being non-judgmental (Kabat-Zinn, 2003). Therefore, it would be helpful to compare emotion introspection and mindful emotion regulation in one sample to draw further conclusions on the differences and communalities of the two tasks. The first study is further limited by the small sample size, even though we used a within-subject design. Furthermore, the depressive patients were only tested without emotional stimulation. The generalization is strongly limited, as it remains possible that the patients would have failed or would have performed less successfully when stimulated. The ability to perform mindfulness might be restricted to instructed situations, not given insight into the capability to a spontaneous engagement. The choice of between-groups design in the second study is also a limiting factor, as unaccounted group differences might have influenced the results. Nevertheless, this approach was chosen to prevent subjects from mixing the strategies.

4.4. Future research

It is of great interest to combine the two presented studies in a future research project, investigating mindful emotion regulation in acutely and remitted depressed patients. This could help to clarify whether the ability of this group to perform mindfulness persists also in confrontation with emotionally arousing stimuli and whether differences arise depending on the state of depression. In the context of psychotherapy, results can help identifying promising treatment strategies for the different subgroups of depressed patients. For example, MBCT was originally designed to prevent relapse in remitted depressed patients (Segal et al., 2002). Recent studies show that acutely depressed patients also have the ability to engage in mindfulness and profit from a MBCT (van Aalderen et al., 2012).

Future research could address the question whether mindfulness is an effective treatment component in response-focused emotion regulation situations, especially if the emotion arising event has happened earlier and with some time elapsed negative emotions persists. The context of traumata and post-traumatic stress disorder, often comorbid with major depressive disorder (Campbell et al., 2007), could therefore be investigated. Previous research indicates that trait mindfulness is associated with fewer PTSD symptoms and depressive symptoms (Smith et al., 2011), but on the other hand other research showed no difference in PTSD symptoms regardless whether participants did Vipanassa mediation course or not (Simpson et al., 2007). Neuropsychological research in this field is still rare, but can be a promising step to elucidate the neurobiological underpinnings of mindfulness and its ways of action. Research might be used to identify therapy-responders and non-responders and thus support the development of an individualized, evidence-based psychotherapeutic treatment.

4.5. Concluding remarks

The results are well in line with previous studies, proposing an involvement of lateral prefrontal areas and a reduction of amygdala activation during mindfulness (Burklund et al., 2014; Herwig et al., 2010; Lieberman et al., 2007). This thesis further expands these findings as it investigated mindfulness in acutely and remitted depressed patients and in healthy subjects in confrontation to emotional stimuli compared to a cognitive control strategy. It provided evidence that patients in the acute and remitted state of depression can engage in mindfulness. The research revealed that mindfulness activates a similar neural activation network as cognitive reappraisal and can be assumed to have a comparable emotion regulating effect. Therefore, the results of this thesis can be regarded as puzzle pieces being added and integrated into the bigger picture of mindfulness research, but they also point out the numerous open questions that need to be solved for a complete understanding of the old, but in terms of research young, construct of mindfulness.

5. Curriculum Vitae

Personal Details

Full name	Sarah Opialla (formerly Sarah Hänert)
Date of Birth	11/21/1983
Place of Birth	Eckernförde, Germany

Employments

Since 2011	Research associate in the research project "Emotion regulation"(Prof. Dr. med. U. Herwig), University of Zurich (CH)
Since 2011	Psychologist at the Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry, Zurich (CH)

Education

2004 – 2006	Basic studies of psychology at the Ernst-Moritz-Arndt University, Greifswald (DE)
2006 – 2007	Main studies of psychology at the Universidad de Granada (ES), ERASMUS scholarship
2007 – 2010	Main studies of psychology with course specialization on clinical psychology at the Humboldt-University, Berlin (DE) Degree: Diplom-Psychologin

Peer-reviewed publications

Opialla, S., Lutz, J., Scherpiet, S., Hittmeyer, A., Jäncke, L., Rufer, M., Grosse Holtforth, M., Herwig, U., Brühl, A.B. (2014). Neural circuits of emotion regulation: A comparison of mindfulness-based and cognitive reappraisal strategies. *European Archives of Psychiatry and Clinical Neuroscience*.

Lutz, J.; Herwig, U.; **Opialla, S.**; Hittmeyer, A.; Jäncke, L.; Rufer, M.; Grosse Holtforth, M.; Brühl, Annette B. (2014): Mindfulness and Emotion Regulation - an fMRI Study. *Social Cognitive and Affective Neuroscience*, (9), 776–785.

Scherpiet, S.; Brühl, A.B.; **Opialla, S.**; Roth, L.; Jäncke, L.; Herwig, U. (in-press): Altered emotion processing circuits during the anticipation of emotional stimuli in women with borderline personality disorder. *European Archives of Psychiatry and Clinical Neuroscience*.

Poster presentations and talks

Opialla, S., Herwig, U., Scherpiet, S., Hittmeyer, A., Cattapan, K., Jäncke, L., Brühl, A.B. (2013): Neurofunktionelle Korrelate von Selbstreflexion und Emotionsintrospektion bei Patienten in depressivem und remittiertem Zustand. DGPPN, November 27-30, 2013, Berlin, Germany.

Scherpiet, S., Brühl, A.B., **Opialla, S.**, Scheerer, H., Lutz, J., Jäncke, L., Herwig, U. (2013): Selbstreferenzielle Hirnaktivität bei Patientinnen mit einer Borderline-Persönlichkeitsstörung. DGPPN, November 27-30, 2013, Berlin, Germany.

Scherpiet, S.; Brühl, A.B.; **Opialla, S.**; Scheerer, H.; Lutz, J.; Jäncke, L.; Herwig, U. (2013): Selbstreferenz und Emotionsregulation bei Patientinnen mit einer Borderline-

Persönlichkeitsstörung. Jahreskongress der Schweizerischen Gesellschaft für Psychiatrie und Psychotherapie, September 13-15, 2013, Montreux, Switzerland.

Opialla, S.; Herwig, U.; Scherpiet, S.; Hittmeyer, A.; Cattapan, K.; Jäncke, L.; Brühl, A. (2013): Neurofunktionelle Korrelate von Selbstreflexion und Emotionsintrospektion bei Patienten in depressivem und remittierten Zustand. Jahreskongress der Schweizerischen Gesellschaft für Psychiatrie und Psychotherapie, September 13-15, 2013, Montreux, Switzerland.

Scherpiet S., Roth L., **Hänert S.**, Brühl A.B., Herwig U. (2012): Neuronale Defizite während der Antizipation von negativen Stimuli in Borderline-Persönlichkeitsstörung. Tag der Forschung der Psychiatrie und Kinder- und Jugendpsychiatrie Zürich, December 12, 2012, Zurich, Switzerland.

Brühl, A.B., Scherpiet, S., Roth, L., **Hänert, S.**, Stämpfli, P., Sulzer, J., Seifritz, E., Herwig, U. (2012): Emotionsregulation durch Echtzeit-fMRT-Neurofeedback der Amygdala-Aktivität. Tag der Forschung der Psychiatrie und Kinder- und Jugendpsychiatrie Zürich, December 12, 2012, Zurich, Switzerland.

Hänert, S., Lutz, J., Scherpiet, S., Hittmeyer, A., Jäncke, L., Rufer, M., Grosse Holtforth, M., Herwig, U., Brühl, A.B.(2012): Achtsamkeitsbasierte und kognitive Emotionsregulation – ein neurofunktioneller Vergleich. Tag der Forschung der Psychiatrie und Kinder- und Jugendpsychiatrie Zürich, December 12, 2012, Zurich, Switzerland.

Scherpiet, S., Roth, L., **Hänert, S.**, Brühl, B., Herwig, U. (2012): Neurobiologische Mechanismen der Emotionsverarbeitung während der Erwartung emotionaer Stimuli bei Patienten mit Borderline-Persönlichkeitsstörung: Eine fMRT-Studie. Jahrestagung

der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN), November 23, 2012, Berlin, Germany.

Brühl, A., Scherpiet, S., Roth, L., **Hänert, S.**, Stämpfli, P., Sulzer, J., Seifritz, E., Herwig, U. (2012): Emotionsregulation durch Echtzeit-fMRT-Neurofeedback der Amygdala-Aktivität. Jahrestagung der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN), November 25, 2012, Berlin, Germany.

Hänert, S., Lutz, J., Hittmeyer, A., Jäncke, L., Rufer, M., Grosse Holtforth, M., Herwig, U., Brühl, A. (2012): Achtsamkeitsbasierte und kognitive Emotionsregulation – ein Vergleich auf neurofunktioneller Ebene. Jahrestagung der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN), November 25, Berlin, Germany

Hänert, S., Lutz, J., Hittmeyer, A., Jäncke, L., Rufer, M., Grosse Holtforth, M., Herwig, U., Brühl, A. (2012): Achtsamkeitsbasierte und kognitive Emotionsregulation – ein neurofunktioneller Vergleich. Jahreskongress der Schweizerischen Gesellschaft für Psychiatrie und Psychotherapie, September 12-14, 2012, Interlaken, Switzerland. Poster Award (3. Place).

Scherpiet, S., Roth, L., **Hänert, S.**, Brühl, A.B., Herwig, U. (2012) Neurobiologische Mechanismen der Emotionsverarbeitung während der Erwartung emotionaler Stimuli bei Patienten mit einer Borderline-Pesönlichkeitsstörung: Eine fMRT Studie. Jahreskongress der Schweizerischen Gesellschaft für Psychiatrie und Psychotherapie, September 12-14, 2012, Interlaken, Switzerland.

Herwig, U., Hittmeyer, A., **Hänert, S.**, Scherpiet, S., Wanner, C., Brühl, A. (2012): Self-reference and emotion regulation in patients suffering from depression. 20th

European Congress on Psychiatry, March 3-6, 2012, Prag, Czech Republic. Best Poster Award.

Brühl, A.B., Scherpiet, S., Roth, L., Sulzer, J., Stämpfli, P., Leiberg, S., **Hänert, S.**, Seifritz, S., Herwig, U. (2012): Training to regulate the amygdala by means of real-time fMRI neurofeedback, 1st Swiss rtfMRI Neurofeedback Conference, February 2, 2012, ETH Zurich, Zurich, Switzerland.

Brühl, A.B., Lutz, J., **Hänert, S.**, Hittmeyer, A., Russmann, H., Jäncke, L., Rufer, M., Grosse-Holtforth, M., Herwig, U. (2011): Neurobiologische Mechanismen der achtsamen Emotionsregulation während der Erwartung emotionaler Stimuli: Eine funktionelle Magnetresonanztomographie-Studie. Jahrestagung der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN), November 24, 2011, Berlin, Germany.

Herwig, U., Wetter, T., Cattapan, K., Hittmeyer, A., **Hänert, S.,** Brühl, A. (2011): Selbstreferenz und Emotionsregulation bei depressiven Patienten. Jahrestagung der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN), November 24, 2011, Berlin, Germany.

Brühl, A. B., Lutz, J., **Hänert, S.,** Hittmeyer, A., Scherpiet, S., Russmann, H., Jäncke, L., Rufer, M., Grosse-Holtforth, M., Herwig, U. (2011): Neurobiologische Mechanismen der achtsamen Emotionsregulation während der Erwartung emotionaler Stimuli: Eine funktionelle Magnetresonanztomographie-Studie. Tag der Forschung der Psychiatrie und Kinder- und Jugendpsychiatrie Zürich, December 9, 2011, Zurich, Switzerland.

Herwig, U., Wetter, Th., Cattapan, K., Hittmeyer, A., Wanner, C., **Hänert, S.,** Brühl, A. B. (2011): Selbstreferenz und Emotionsregulation bei depressiven Patienten. Tag der

Forschung der Psychiatrie und Kinder- und Jugendpsychiatrie Zürich, December 9, 2011, Zurich, Switzerland.

Hänert, S., Giljohann, S., Volbert, R. (2011): The Influence of Translations on Text-Based Credibility Assessment. 4th International Congress on Psychology and Law, March 2-6, 2011, Miami, United States of America. EAPL-S-Award (Best Research Paper).

Hänert, S., Giljohann, S., Volbert, R. (2010): Der Einfluss von Übersetzungen auf textbasierte Glaubhaftigkeitsattributionen. 47. Kongress der Deutschen Gesellschaft für Psychologie, September 26-30, 2010, Bremen.

6. References

Aldao, A., Nolen-Hoeksema, S., Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review*, *30*(2), 217–237. doi:10.1016/j.cpr.2009.11.004

Allen, M., Dietz, M., Blair, K. S., van Beek, M., Rees, G., Vestergaard-Poulsen, P., Lutz, A., Roepstorff, A. (2012). Cognitive-Affective Neural Plasticity following Active-Controlled Mindfulness Intervention. *Journal of Neuroscience*, *32*(44), 15601–15610. doi:10.1523/JNEUROSCI.2957-12.2012

Beauregard, M., Paquette, V., Lévesque, J. (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *Neuroreport*, *17*(8), 843–846. doi:10.1097/01.wnr.0000220132.32091.9f

Beck, A. T., Dozois, D. J. (2011). Cognitive Therapy: Current Status and Future Directions. *Annual Review of Medicine*, *62*(1), 397–409. doi:10.1146/annurev-med-052209-100032

Beck, A. T., Rush, A. J., Shaw, B. F., Emery, G. (1979). *Cognitive therapy of depression*. *Guilford clinical psychology and psychotherapy series*. New York: Guilford Press.

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., Segal, Z. V., Abbey, S., Speca, M., Velting, D., Devins, G. (2004). Mindfulness: A Proposed Operational Definition. *Clinical Psychology: Science and Practice*, *11*(3), 230–241. doi:10.1093/clipsy.bph077

Bohus, M., Wolf-Arehult, M. (2011). *Interaktives SkillsTraining für Borderline-Patienten: Manual zur CD-ROM für die therapeutische Arbeit*. Stuttgart: Schattauer.

Borkovec, T. D. (2002). Life in the Future Versus Life in the Present. *Clinical Psychology: Science and Practice*, *9*(1), 76–80. doi:10.1093/clipsy.9.1.76

Brown, K. W., Ryan, R. M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology*, *84*(4), 822–848. doi:10.1037/0022-3514.84.4.822

Brühl, A. B. (2012). *Neurofunktionelle Mechanismen der Emotionsregulation bei Gesunden und bei affektiven Erkrankungen.* Habiliationsschrift. University of Zurich.

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., Ochsner, K. N. (2013). Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. *Cerebral Cortex.* doi:10.1093/cercor/bht154

Burklund, L. J., Creswell, J. D., Irwin, M. R., Lieberman, M. D. (2014). The common and distinct neural bases of affect labeling and reappraisal in healthy adults. *Frontiers in Psychology*, *5.* doi:10.3389/fpsyg.2014.00221

Cahn, B. R., Polich, J. (2006). Meditation states and traits: EEG, ERP, and neuroimaging studies. *Psychological Bulletin*, *132*(2), 180–211. doi:10.1037/0033-2909.132.2.180

Campbell, D. G., Felker, B. L., Liu, C.-F., Yano, E. M., Kirchner, J. E., Chan, D., Rubenstein, L.V., Chaney, E. F. (2007). Prevalence of Depression–PTSD Comorbidity: Implications for Clinical Practice Guidelines and Primary Care-based Interventions. *Journal of General Internal Medicine*, *22*(6), 711–718. doi:10.1007/s11606-006-0101-4

Chambers, R., Gullone, E., Hassed, C., Knight, W., Garvin, T., Allen, N. (2014). Mindful Emotion Regulation Predicts Recovery in Depressed Youth. *Mindfulness.* doi:10.1007/s12671-014-0284-4

Chambers, R., Lo, B. C., Allen, N. B. (2008). The Impact of Intensive Mindfulness Training on Attentional Control, Cognitive Style, and Affect. *Cognitive Therapy and Research*, *32*(3), 303–322. doi:10.1007/s10608-007-9119-0

Chambless, D. L., Ollendick, T. H. (2001). Empirically supported psychological interventions: controversies and evidence. *Annual review of psychology*, *52*, 685–716. doi:10.1146/annurev.psych.52.1.685

Chiesa, A. (2013). The Difficulty of Defining Mindfulness: Current Thought and Critical Issues. *Mindfulness*, *4*(3), 255–268. doi:10.1007/s12671-012-0123-4

Chiesa, A., Serretti, A. (2010). A systematic review of neurobiological and clinical features of mindfulness meditations. *Psychological Medicine*, *40*(08), 1239–1252. doi:10.1017/S0033291709991747

Cooney, R. E., Joormann, J., Eugène, F., Dennis, E. L., Gotlib, I. H. (2010). Neural correlates of rumination in depression. *Cognitive, Affective, & Behavioral Neuroscience*, *10*(4), 470–478. doi:10.3758/CABN.10.4.470

Creswell, J. D., Way, B. M., Eisenberger, N. I., Lieberman, M. D. (2007). Neural Correlates of Dispositional Mindfulness During Affect Labeling. *Psychosomatic Medicine*, *69*(6), 560–565. doi:10.1097/PSY.0b013e3180f6171f

Davis, D. M., Hayes, J. A. (2011). What are the benefits of mindfulness? A practice review of psychotherapy-related research. *Psychotherapy*, *48*(2), 198–208. doi:10.1037/a0022062

Dickenson, J., Berkman, E. T., Arch, J., Lieberman, M. D. (2013). Neural correlates of focused attention during a brief mindfulness induction. *Social Cognitive and Affective Neuroscience*, *8*(1), 40–47. doi:10.1093/scan/nss030

Diekhof, E. K., Geier, K., Falkai, P., Gruber, O. (2011). Fear is only as deep as the mind allows. *NeuroImage*, *58*(1), 275–285. doi:10.1016/j.neuroimage.2011.05.073

Disner, S. G., Beevers, C. G., Haigh, E. A. P., Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, *12*(8), 467–477. doi:10.1038/nrn3027

Edelman, R. R. (Ed.). (2006). *Clinical magnetic resonance imaging* (3. ed). Philadelphia, Pa: Saunders Elsevier.

Ellis, A. (2008). *Grundlagen und Methoden der rational-emotiven Verhaltenstherapie* (2. Aufl). *Leben lernen: Vol. 26*. Stuttgart: Klett-Cotta.

Farb, N. A. S., Anderson, A. K., Mayberg, H., Bean, J., McKeon, D., Segal, Z. V. (2010). Minding one’s emotions: Mindfulness training alters the neural expression of sadness. *Emotion*, *10*(1), 25–33. doi:10.1037/a0017151

Farb, N. A. S., Segal, Z. V., Mayberg, H., Bean, J., McKeon, D., Fatima, Z., Anderson, A. K. (2007). Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience*, *2*(4), 313–322. doi:10.1093/scan/nsm030

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., Vos, T.; Whiteford, H. A., Hay, P. J. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Medicine*, *10*(11), e1001547. doi:10.1371/journal.pmed.1001547

Fjorback, L. O., Arendt, M., Ørnbøl, E., Fink, P., Walach, H. (2011). Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy - a systematic review of randomized controlled trials. *Acta Psychiatrica Scandinavica*, *124*(2), 102–119. doi:10.1111/j.1600-0447.2011.01704.x

Goel, V., Dolan, R. J. (2001). The functional anatomy of humor: segregating cognitive and affective components. *Nature neuroscience*, *4*(3), 237–238. doi:10.1038/85076

Goldin, P., Ziv, M., Jazaieri, H., Hahn, K., Gross, J. J. (2013). MBSR vs aerobic exercise in social anxiety: fMRI of emotion regulation of negative self-beliefs. *Social Cognitive and Affective Neuroscience*, *8*(1), 65–72. doi:10.1093/scan/nss054

Goldin, P. R., McRae, K., Ramel, W., Gross, J. J. (2008). The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion. *Biological Psychiatry*, *63*(6), 577–586. doi:10.1016/j.biopsych.2007.05.031

Grimm, S., Ernst, J., Boesiger, P., Schuepbach, D., Hell, D., Boeker, H., Northoff, G. (2009). Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. *Human Brain Mapping*, *30*(8), 2617–2627. doi:10.1002/hbm.20693

Gross, J. J. (1998). Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology*, *74*(1), 224–237.

Gross, J. J., John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology*, *85*(2), 348–362. doi:10.1037/0022-3514.85.2.348

Gross, J. J., Thompson, R. A. (2007). Emotion regulation: conceptual foundations. In J. J. Gross (Ed.), *Handbook of emotion regulation* (pp. 3–26). New York, NY: Guilford Press.

Gross, J. J. (Ed.). (2007). *Handbook of emotion regulation*. New York, NY: Guilford Press.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*, (23), 56–62.

Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *NeuroImage*, *59*(1), 750–760. doi:10.1016/j.neuroimage.2011.07.008

Henry, J. D., Rendell, P. G., Green, M. J., McDonald, S., O'Donnell, M. (2008). Emotion regulation in schizophrenia: Affective, social, and clinical correlates of suppression and reappraisal. *Journal of Abnormal Psychology*, *117*(2), 473–478. doi:10.1037/0021-843X.117.2.473

Herwig, U., Baumgartner, T., Kaffenberger, T., Brühl, A., Kottlow, M., Schreiter-Gasser, U.,Abler, B., Jäncke, L., Rufer, M. (2007). Modulation of anticipatory emotion and perception processing by cognitive control. *NeuroImage*, *37*(2), 652–662. doi:10.1016/j.neuroimage.2007.05.023

Herwig, U., Brühl, A. B., Kaffenberger, T., Baumgartner, T., Boeker, H., Jäncke, L. (2010). Neural correlates of ‘pessimistic’ attitude in depression. *Psychological Medicine*, *40*(05), 789. doi:10.1017/S0033291709991073

Herwig, U., Kaffenberger, T., Jäncke, L., Brühl, A. B. (2010). Self-related awareness and emotion regulation. *NeuroImage*, *50*(2), 734–741. doi:10.1016/j.neuroimage.2009.12.089

Hofmann, S. G., Asnaani, A., Vonk, I. J. J., Sawyer, A. T., Fang, A. (2012). The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognitive Therapy and Research*, *36*(5), 427–440. doi:10.1007/s10608-012-9476-1

Hölzel, B. K., Ott, U., Hempel, H., A., Wolf, K., Stark, R., Vaitl, D. (2007). Differential engagement of anterior cingulate and adjacent medial frontal cortex in adept meditators and non-meditators. *Neuroscience Letters*, *421*(1), 16–21. doi:10.1016/j.neulet.2007.04.074

Huffziger, S., Kuehner, C. (2009). Rumination, distraction, and mindful self-focus in depressed patients. *Behaviour Research and Therapy*, *47*(3), 224–230. doi:10.1016/j.brat.2008.12.005

Ives-Deliperi, V. L., Solms, M., Meintjes, E. M. (2011). The neural substrates of mindfulness: An fMRI investigation. *Social Neuroscience*, *6*(3), 231–242. doi:10.1080/17470919.2010.513495

Jäncke, L. (2013). *Lehrbuch Kognitive Neurowissenschaften* (1., Originalausgabe). *Lehrbuch Psychologie*. Bern: Verlag Hans Huber.

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., Davidson, R. J. (2007). Failure to Regulate: Counterproductive Recruitment of Top-Down Prefrontal-Subcortical Circuitry in Major Depression. *Journal of Neuroscience*, *27*(33), 8877–8884. doi:10.1523/JNEUROSCI.2063-07.2007

Kabat-Zinn, J. (2003). Mindfulness-Based Interventions in Context: Past, Present, and Future. *Clinical Psychology: Science and Practice*, *10*(2), 144–156. doi:10.1093/clipsy.bpg016

Kabat-Zinn, J., Wheeler, E., Light, T., Skillings, A., Scharf, M. J., Cropley, T. G., Hosmer, D., Bernhard, J. D. (1998). Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). *Psychosomatic medicine*, *60*(5), 625–632.

Kalisch, R. (2009). The functional neuroanatomy of reappraisal: Time matters. *Neuroscience & Biobehavioral Reviews*, *33*(8), 1215–1226. doi:10.1016/j.neubiorev.2009.06.003

Kanske, P., Heissler, J., Schonfelder, S., Bongers, A., Wessa, M. (2011). How to Regulate Emotion? Neural Networks for Reappraisal and Distraction. *Cerebral Cortex*, *21*(6), 1379–1388. doi:10.1093/cercor/bhq216

Khoury, B., Lecomte, T., Fortin, G., Masse, M., Therien, P., Bouchard, V., Chapleau, M.-A., Paquin, K., Hofmann, S. G. (2013). Mindfulness-based therapy: A comprehensive meta-analysis. *Clinical Psychology Review*, *33*(6), 763–771. doi:10.1016/j.cpr.2013.05.005

Koenigs, M., Grafman, J. (2009). The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research*, *201*(2), 239–243. doi:10.1016/j.bbr.2009.03.004

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., Habel, U. (2014). Neural network of cognitive emotion regulation - An ALE meta-analysis and MACM analysis. *NeuroImage*, *87*, 345–355. doi:10.1016/j.neuroimage.2013.11.001

Kring, A. M., Sloan, D. M. (Eds.). (2010). *Emotion regulation and psychopathology: A transdiagnostic approach to etiology and treatment*. New York, NY: Guilford Press.

Lemogne, C., Delaveau, P., Freton, M., Guionnet, S., Fossati, P. (2012). Medial prefrontal cortex and the self in major depression. *Journal of Affective Disorders*, *136*(1-2), e1–e11. doi:10.1016/j.jad.2010.11.034

Lemogne, C., Mayberg, H., Bergouignan, L., Volle, E., Delaveau, P., Lehéricy, S., Allilaire, J.-F., Fossati, P. (2010). Self-referential processing and the prefrontal cortex over the course of depression: A pilot study. *Journal of Affective Disorders*, *124*(1-2), 196–201. doi:10.1016/j.jad.2009.11.003

Lieberman, M. D., Eisenberger, N. I., Crockett, M. J., Tom, S. M., Pfeifer, J. H., Way, B. M. (2007). Putting Feelings Into Words: Affect Labeling Disrupts Amygdala Activity in Response to Affective Stimuli. *Psychological Science*, *18*(5), 421–428. doi:10.1111/j.1467-9280.2007.01916.x

Linehan, M. (1993). *Skills training manual for treating borderline personality disorder*. *Diagnosis and treatment of mental disorders*. New York u.a: Guilford Press.

Lutz, J., Herwig, U., Opialla, S., Hittmeyer, A., Jancke, L., Rufer, M., Grosse Holtforth, M., Brühl, A. B. (2014). Mindfulness and emotion regulation--an fMRI study. *Social Cognitive and Affective Neuroscience*, (9), 776–785. doi:10.1093/scan/nst043

Middleton, F. (2000). Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Research Reviews*, *31*(2-3), 236–250. doi:10.1016/S0165-0173(99)00040-5

Monk, C. S. (2008). The development of emotion-related neural circuitry in health and psychopathology. *Development and Psychopathology*, *20*(04), 1231. doi:10.1017/S095457940800059X

Montgomery, S. A., Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382–389. doi:10.1192/bjp.134.4.382

Morin, A., Hamper, B. (2012). Self-Reflection and the Inner Voice: Activation of the Left Inferior Frontal Gyrus During Perceptual and Conceptual Self-Referential Thinking. *The Open Neuroimaging Journal*, *6*, 78–89. doi:10.2174/1874440001206010078

Nesse, R. M. (2000). Is Depression an Adaptation? *Archives of General Psychiatry*, *57*(1), 14. doi:10.1001/archpsyc.57.1.14

Northoff, G. (2007). Psychopathology and pathophysiology of the self in depression — Neuropsychiatric hypothesis. *Journal of Affective Disorders*, *104*(1-3), 1–14. doi:10.1016/j.jad.2007.02.012

Ochsner, K. N., Bunge, S. A., Gross, J. J., Gabrieli, J. D. E. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*(8), 1215–1229. doi:10.1162/089892902760807212

Ochsner, K. N., Gross, J. J. (2007). The neural architecture of emotion regulation. In J. J. Gross (Ed.), *Handbook of emotion regulation* (pp. 87–109). New York, NY: Guilford Press.

Ochsner, K. N., Gross, J. J. (2008). Cognitive Emotion Regulation: Insights From Social Cognitive and Affective Neuroscience. *Current Directions in Psychological Science*, *17*(2), 153–158. doi:10.1111/j.1467-8721.2008.00566.x

Ramana, R., Paykel, E. S., Cooper, Z., Hayhurst, H., Saxty, M., Surtees, P. G. (1995). Remission and relapse in major depression: a two-year prospective follow-up study. *Psychological Medicine*, *25*(06), 1161. doi:10.1017/S0033291700033134

Segal, Z. V., Williams, J. M. G, Teasdale, J. D. (2013). *Mindfulness-based cognitive therapy for depression* (2nd ed). New York: Guilford Press.

Segal, Z. V., Williams, J. M. G., Teasdale, J. D. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse* (5. print). New York u.a: Guilford Press.

Shapiro, S. L., Brown, K. W., Thoresen, C., Plante, T. G. (2011). The moderation of Mindfulness-based stress reduction effects by trait mindfulness: Results from a randomized controlled trial. *Journal of Clinical Psychology*, *67*(3), 267–277. doi:10.1002/jclp.20761

Shapiro, S. L., Carlson, L. E., Astin, J. A., Freedman, B. (2006). Mechanisms of mindfulness. *Journal of Clinical Psychology*, *62*(3), 373–386. doi:10.1002/jclp.20237

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G. C. (1998). The Mini-International. Neuropsychiatric Interview (M.I.N.I): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*(suppl.20), 22–33.

Simpson, T. L., Kaysen, D., Bowen, S., MacPherson, L. M., Chawla, N., Blume, A., Marlatt, G. A., Larimer, M. (2007). PTSD symptoms, substance use, and vipassana meditation among incarcerated individuals. *Journal of Traumatic Stress*, *20*(3), 239–249. doi:10.1002/jts.20209

Smith, B. W., Ortiz, J. A., Steffen, L. E., Tooley, E. M., Wiggins, K. T., Yeater, E. A., Montoya, J. D., Bernard, M. L. (2011). Mindfulness is associated with fewer PTSD symptoms, depressive symptoms, physical symptoms, and alcohol problems in urban firefighters. *Journal of Consulting and Clinical Psychology*, *79*(5), 613–617. doi:10.1037/a0025189

Soares, J. C., Mann, J. J. (1997). The functional neuroanatomy of mood disorders. *Journal of Psychiatric Research*, *31*(4), 393–432. doi:10.1016/S0022-3956(97)00016-2

Tang, Y.-Y., Ma, Y., Wang, J., Fan, Y., Feng, S., Lu, Q.,Yu, Q., Sui, D., Rothbart, M. K., Posner, M. I. (2007). Short-term meditation training improves attention and self-regulation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(43), 17152–17156. doi:10.1073/pnas.0707678104

Taylor, V. A., Grant, J., Daneault, V., Scavone, G., Breton, E., Roffe-Vidal, S., Courtemanche, J., Lavarenne, A. S., Beauregard, M. (2011). Impact of mindfulness on the neural responses to emotional pictures in experienced and beginner meditators. *NeuroImage*, *57*(4), 1524–1533. doi:10.1016/j.neuroimage.2011.06.001

Uludag, K., Dubowitz, D. J., Buxton, R. B. (2006). Basic principles of functional MRI. In R. R. Edelman (Ed.), *Clinical magnetic resonance imaging* (3rd ed., pp. 249–287). Philadelphia, Pa: Saunders Elsevier.

van Aalderen, J. R., Donders, A. R. T., Giommi, F., Spinhoven, P., Barendregt, H. P., Speckens, A. E. M. (2012). The efficacy of mindfulness-based cognitive therapy in recurrent depressed patients with and without a current depressive episode: a randomized controlled trial. *Psychological Medicine*, *42*(05), 989–1001. doi:10.1017/S0033291711002054

Visser, M., Lambon Ralph, M. A. (2011). Differential Contributions of Bilateral Ventral Anterior Temporal Lobe and Left Anterior Superior Temporal Gyrus to Semantic Processes. *Journal of Cognitive Neuroscience*, *23*(10), 3121–3131. doi:10.1162/jocn_a_00007

Webb, T. L., Miles, E., Sheeran, P. (2012). Dealing with feeling: A meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. *Psychological Bulletin*, *138*(4), 775–808. doi:10.1037/a0027600

Werner, K., Gross, J. J. (2010). Emotion regulation and psychopathology: A conceptual framework. In A. M. Kring & D. M. Sloan (Eds.), *Emotion regulation and psychopathology. A transdiagnostic approach to etiology and treatment* (pp. 13–37). New York, NY: Guilford Press.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., Jefferies, E. (2011). The Neural Organization of Semantic Control: TMS Evidence for a Distributed Network in Left Inferior Frontal and Posterior Middle Temporal Gyrus. *Cerebral Cortex*, *21*(5), 1066–1075. doi:10.1093/cercor/bhq180

Williams, J., Alatiq, Y., Crane, C., Barnhofer, T., Fennell, M., Duggan, D. S., Hepburn, S., Goodwin, G. M. (2008). Mindfulness-based Cognitive Therapy (MBCT) in bipolar disorder: Preliminary evaluation of immediate effects on between-episode functioning. *Journal of Affective Disorders*, *107*(1-3), 275–279. doi:10.1016/j.jad.2007.08.022

World Health Organization. (2012). *Depression*. Retrieved July 28, 2014 from http://www.who.int/mediacentre/factsheets/fs369/en/

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato, Y., Yoshino, A., Ueda, K., Suzuki, S.-I., Yamawaki, S. (2013). Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Social Cognitive and Affective Neuroscience.* doi:10.1093/scan/nst009

Zhang, J., Hughes, L. E., Rowe, J. B. (2012). Selection and inhibition mechanisms for human voluntary action decisions. NeuroImage, 63(1), 392–402. doi:10.1016/j.neuroimage.2012.06.058